Organic Process Research & Development

ARTICLE

pubs.acs.org/OPRD

Synthesis of the Hepatitis B Nucleoside Analogue Lagociclovir Valactate

Martin Brodszki,[†] Birthe Bäckström,[†] Karol Horvath,[§] Torbjörn Larsson,[‡] Håkan Malmgren,[†] Mikael Pelcman,[‡] Horst Wähling,[‡] Hans Wallberg,[‡] and Johan Wennerberg*[,†]

[†]DuPont Chemoswed, R&D, P.O. Box 839, SE-201 80 Malmö, Sweden

[‡]Medivir AB, P.O. Box 1086, SE-141 22 Huddinge, Sweden

[§]KH Crystallization Service, Fornhöjdsvägen 56, SE-152 58 Södertälje, Sweden

ABSTRACT: 2′,3′-Dideoxy-3′-fluoro-5-*O*-[(S)-(+)-2-(L-valyloxy)-propionyl] guanosine (lagociclovir valactate) is a prodrug of 3′-fluoro-2′,3′-dideoxyguanosine with high oral bioavailability in humans and potent activity against hepatitis B virus (HBV). A five-step synthesis of lagocyclovir valactate starting from 2-amino-6-chloropurine is described. The synthesis was performed at kilogram scale, and the target nucleoside prodrug was isolated as the hemisulphate salt with an overall yield of 23%. The major challenges were N-glycosylation of a 2-deoxyfluorosugar, which required separation of α- and β-anomers, and deprotection of the penultimate intermediate by hydrogenation.

INTRODUCTION

Lagociclovir valactate (2′,3′-dideoxy-3′-fluoro-5-*O*-[(*S*)-(+)-2-(L-valyloxy)-propionyl] guanosine)[1] (**1**), a prodrug of FLG (3′-fluoro-2′,3′-dideoxyguanosine) (**2**), has shown excellent pharmacokinetic properties in phase 1 clinical studies.[2] After absorption, lagociclovir valactate is converted to the nucleoside **2** which is phosphorylated to the active metabolite FLG triphosphate. FLG triphosphate is a competitive inhibitor which inhibits HBV DNA-polymerase by competition with the natural substrate (deoxyguanosine triphosphate, dGTP) and causes chain termination. It has been demonstrated in vitro that FLG exhibits similar inhibitory activity on wild type as well as single- and multiple-drug-resistant HBV mutants arising from adefovir and lamuvidine.[3] Adefovir and lamivudine are currently used in treatment of HBV, but both lead to the development of a resistant virus, thereby losing their therapeutic usefulness. The in vitro studies have indicated that the polymerase inhibitor FLG blocks HBV polymerase by a different mechanism than adefovir. FLG has also shown a profound antiviral effect after oral administration in a Woodchuck model for Hepatitis B.[4] Hepatitis B is a common form of jaundice in need of better treatment alternatives than those currently available. FLG is also active against both wild type and multiple-drug-resistant HIV-1, which has a polymerase that resembles the HBV polymerase.[5] To support clinical trials kilogram quantities of **1** were required. The synthetic route developed consists of five synthetic steps followed by salt formation. The most challenging steps were the N-glycosylation of 2-acetoamido-6-chloropurine (**3**) and the deprotection of Cbz intermediate **4** (Scheme 1). In the N-glycosylation step both the α- and the desired β-anomers were formed, which required careful separation. In the deprotection step, the major challenge was to suppress catalyst poisoning. The present method made it possible to manufacture **1** at kilogram scale in high purity whilst conforming to all regulatory requirements.

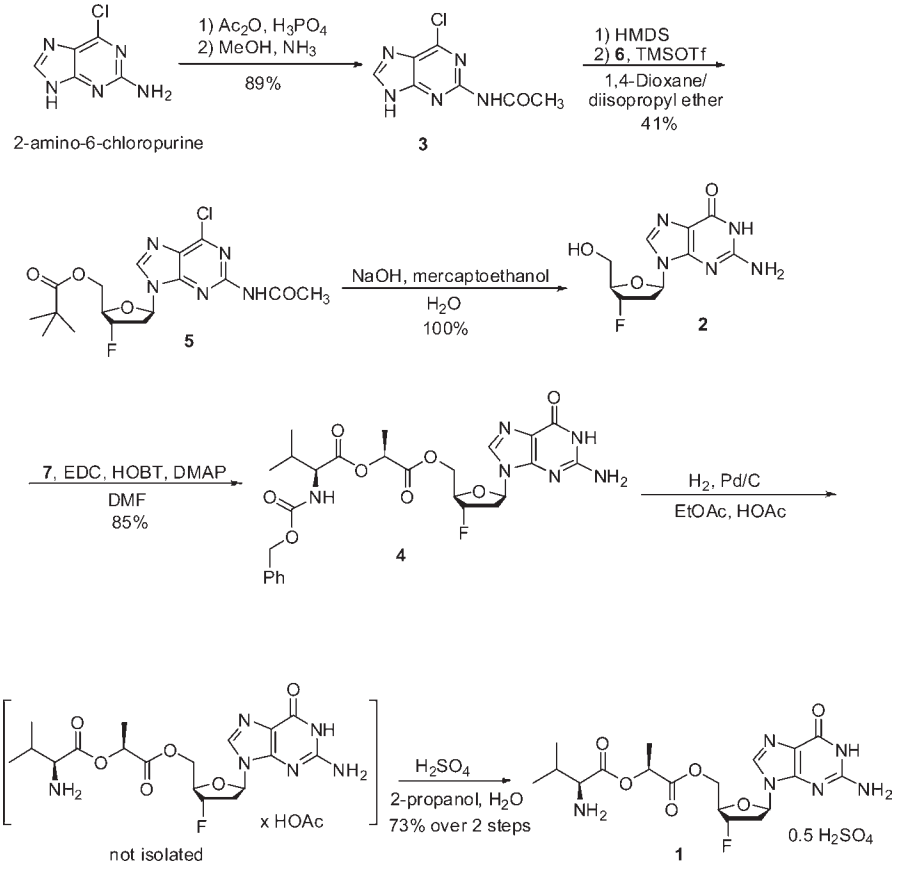
RESULTS AND DISCUSSION

Commercially available 2-amino-6-chloropurine was first converted to its diacetamide, by treatment with acetic anhydride, and promoted by a catalytic amount of phosphoric acid. After evaporation the crude product was partially hydrolyzed in methanol/ammonia.[6] Acetamide **3** precipitated from the solution upon concentration and was collected by centrifugation in 89% yield. The quality of the starting material was found to be a critical factor in determining reaction outcome. 2-Amino-6-chloropurine of 98% purity gave satisfactorily results, but batches of 97% purity resulted in an approximately 15% lower yield. A major drawback for this step was the large amounts of acetic anhydride and ammonia/methanol required; unfortunately the yield was highly dependent on a large excess of these reagents.

N-Glycosylation of **3** to yield **5** was achieved via silylation of **3** followed by reaction with protected 2-deoxyfluorosugar **6**[7] and trimethylsilyl trifluoromethanesulfonate (Scheme 1). Compound **3** was silylated at two positions using 1,1,1,3,3,3-hexamethyldisilazane and a catalytic amount of ammonium sulfate in a mixture of 1,4-dioxane and diisopropyl ether (Figure 1) in order to enhance the nucleophilicity of the N-9 nitrogen participating in the glycosylation.[8] The silylated intermediate was reacted with 2-deoxyfluorosugar **6** using a stoichiometric amount of trimethylsilyl trifluoromethanesulfonate (scheme 1). After workup the product was obtained as a mixture of the α- and β-anomers in a 47/53 ratio. The difference in R_f value on silica gel TLC plates was 0.1, and careful normal phase chromatography resulted in the desired β-anomer **5** in 41% yield. All attempts to purify the material by crystallization were unsuccessful. The glycosylation mechanism should most likely be an S_N1 reaction in which a planar carbocation is formed from 2-deoxyfluorosugar **6** in the rate-determining step. The silylated base can then attack from both sides, which results in an equal or almost equal mixture of anomers. This problem does not appear when using riboses because neighboring group participation of the 2-acyl group directs the incoming nucleophile from the top face, yielding predominantly the β-anomer.[9] It was noted that the pure α-anomer of 2-deoxyfluorosugar **6** undergoes anomerization

Received: June 7, 2011
Published: August 03, 2011

Scheme 1. Synthetic route to lagociclovir valactate



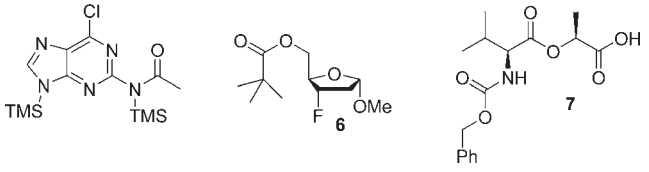


Figure 1. Bis-silylated **3** and starting materials **6** and **7**.

during the reaction conditions. The observed anomerization was very rapid. The conversion of the pure α-anomer to an anomeric mixture required only a few minutes when the α-anomer was treated with trimethylsilyl trifluoromethanesulfonate in 1, 4-dioxane. Anomerization also occurred with hydrogen chloride, although at a slower rate. When α-2-deoxyfluorosugar **6** was dissolved in 1,4-dioxane, without any acid added, anomerization was hardly detected after 1 h. Regarding the kinetics, the α-2-deoxyfluorosugar reacts more slowly than β-2-deoxyfluorosugar and there is a competition between anomerization and glycosylation. It may also be that the use of pure α-2-deoxyfluorosugar is not needed for this reaction (*vide infra*). Anyway, both the anomerization of the starting material and the S_N1 mechanism in the glycosylation will affect the outcome of the reaction in a negative way. The result of the reaction is dependent on the choice of catalyst and solvent. Formation of the undesired α-product **5** is favored by polar solvents, high temperature, and strong Lewis acids; we also found that more diluted conditions favored formation of the α-anomer. A number of different reaction conditions were examined (Table 1). It has been reported that mild Lewis acids such as $ZnCl_2$ and CuI have been used in the synthesis of β-nucleoside anomers, but in these cases chlorosugars were used as starting materials.[9] Experiments with $ZnCl_2$ and CuI gave in our case no conversion of starting material, and anomerization of **6** was not observed even after 18 h (entries 2 and 3); it was determined that $ZnCl_2$ and CuI were too weak as Lewis acids for the present application. BF_3 etherate on the other hand gave **5** with an unfavorable ratio and low conversion (entry 4). Chlorinated solvents have often been applied in this type of reaction,[10] but in our case the use of dichloromethane favored the formation of the undesired α-nucleoside anomer (entry 5). The same outcome was observed for acetonitrile (entry 8). Solvents such as DMF, THF, benzene, toluene, and methanol gave no conversion (entries 6, 7, 9−11). Interestingly acetone gave a favorable α/β ratio but very low conversion (entry 12). Eventually the large scale reaction was run in 1,4-dioxane and diisopropyl ether with TMS-triflate at 20 °C for 20 h.

We also attempted to apply α-halosugars as donors. This reaction would follow an S_N2 mechanism which would lead to inversion of the stereochemistry. The conditions are mild; often catalysts are unnecessary minimizing the risk for anomerization of starting material. Many good results have been reported,[11] but our attempts failed. Although, it was possible to convert α-2-deoxyfluorosugar **6** to the α-chlorosugar,[12] it was not possible to purify. The corresponding α-bromosugar was too labile to be useful. Attempts were also made to use a mixture of α and

dx.doi.org/10.1021/op200153s |*Org. Process Res. Dev.* 2011, 15, 1027–1032

Table 1. Anomeric ratio for 5 under different reaction conditions (selected experiments)[a]

Entry	Solvent	Temp (°C)	Reaction time (h)	α/β Ratio	Conversion[b] α + β (%)
1	Dioxane	21	22	47/53	89
2	Dioxane	21	18	–	no conversion
3	Dioxane	21	18	–	no conversion
4	Dioxane	21	22	68/32	18
5	DCM	21	7	54/46	89
6	DMF	21	24	–	no conversion
7	THF	21	22	–	no conversion
8	Acetonitrile	21	18	58/42	73
9	Benzene	21	24	–	no conversion
10	Toluene	21	24	–	no conversion
11	Methanol	21	18	–	no conversion
12	Acetone	21	18	25/75	5
13	Dioxane + DCM	8	53	44/56	85
14	Dioxane + DCM	−4	30	36/64	79
15	Dioxane + DCM	−13	48	38/62	18

[a] All reactions were performed with TMS-triflate except for entries 2, 3, and 4 which were run with $ZnCl_2$, CuI, and BF_3 etherate, respectively. [b] Conversion was measured with HPLC.

β-2-deoxyfluorosugar **6** as starting material. The yield was in the same range as for the reaction with pure α-2-deoxyfluorosugar **6,** but the purity of the product was not satisfactory. Two impurities, which were impossible to separate from **5** with chromatography, were encountered. The present method made it possible to produce kilogram quantities of **5** with good quality in a yield of 41% (53% theoretically possible) with the low yielding step early on in the synthetic sequence.

In the next step, **5** was treated with 2-mercaptoethanol and sodium hydroxide resulting in cleavage of both protecting groups and conversion of the 6-chloropurine to guanosine[13] (Scheme 1). After neutralization with acetic acid, compound **2** was isolated in quantitative yield.

The Cbz-protected side chain **7**[14] used in the next step was supplied as the dicyclohexylamine salt, which was converted to the free acid by treatment with hydrogen chloride in diethyl ether. For the reaction of **2** and **7** (Scheme 1), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC) was used as a coupling reagent in the presence of 1-hydroxybenzotriazole and dimethylaminopyridine in DMF. This combination of reagents gave **4** with high reproducibility, in high yield and purity. However, to obtain an optimal yield it was required to add the coupling reagent in three portions and carefully monitor the progress of the reaction with HPLC. After workup, the crude material was crystallized from ethanol/diethyl ether, followed by repeated washings with diethyl ether providing **4**. This extensive ether washing procedure was crucial to eliminate an unidentified byproduct in the crude material that was otherwise found to inhibit the subsequent hydrogenation. When the diethyl ether wash residues were concentrated, the impurity was detected as a discrete spot on TLC (R_f 0.67, *n*-heptane−EtOAc 2:3). Despite the tedious procedure the yield was fairly good (85%). Other reagents were also tested including dicyclohexyl carbodiimide, oxalyl chloride, and mixed anhydride. However, these reagents were unsatisfactory in terms of purity, yield, and reproducibility (Table 2). DCC gave a good yield, but chromatography was required despite the apparent high purity (entry 1). Oxalyl chloride showed poor reproducibility, and side reactions were also observed (entry 2). Mixed anhydride formed with pivaloyl chloride showed a consistently low yield (entry 3).

Table 2. Reagents for coupling of 2 and 7[a]

Entry	Coupling reagent	Yield (%)	Purity (area%)
1	DCC	85	98−99[b]
2	Oxalyl chloride[c]	52−95	95−98
3	Pivaloyl chloride	32	very impure
4	EDC	94−95	98

[a] All reactions were performed at small scale (2.5−12.5 mmol). [b] Chromatography was required. [c] Bad reproducibility and occasionally impure due to side reactions.

The Cbz-protecting group was removed from **4** by catalytic hydrogenation with 10% palladium on carbon in a mixture of ethyl acetate and acetic acid to give **8** (Scheme 1). This step turned out to be very difficult; it was necessary to use large amounts of the catalyst to get the reaction to go to completion. However, a 40% reduction of the initial amount of catalyst required was reached during laboratory development. The amount of catalyst required was partly related to the purity of **4** obtained in the previous step. Although the starting material had over 99% purity by HPLC, hydrogenation was sluggish. An unknown impurity, not detected with HPLC, seemed to poison the catalyst (*vide supra*), and treatment with activated charcoal prior to hydrogenation provided no improvement. However, purification of **4** by silica gel chromatography, in laboratory scale, prior to hydrogenation gave a material which was easy to hydrogenate. Reaction for 2 h at 2.7 bar at rt with 25% (w/w) 10% Pd/C gave full conversion. To examine if the impurity had its origin in the 2-mercaptoethanol used to make **2**, experiments were performed in which **4** was treated with hydrogen peroxide or Oxone in order to oxidize sulfur-containing impurities, prior to a screening of hydrogenation conditions.

Palladium on charcoal, palladium black, and palladium hydroxide were tested with different solvents and solvent combinations. Additionally catalysts with different palladium content from different lots and suppliers and acidic conditions as well as transfer hydrogenation conditions were investigated. To our dismay the reactions were uniformly very slow or resulted in no conversion of the starting material. As a comparison, **4** synthesized from sulfur-free **2** also reacted very slowly under hydrogenation conditions. Eventually, after crystallization from ethanol/diethyl ether and repeated washings with diethyl ether, **4** sufficiently pure for hydrogenation was obtained. This material underwent hydrogenolysis with full conversion at 3 bar and 30 °C during 3 h. The major drawback for this procedure was that nearly 50 mol % palladium was required to obtain full conversion, but all further attempts to reduce the amount of palladium led to incomplete conversion. On one occasion the reaction stalled at 60% conversion, and all attempts to continue the reaction by addition of more catalyst failed. After careful examination of all chemicals involved, it was discovered that, after evaporation of "pure" ethyl acetate, an oily residue was obtained, which was the likely culprit of catalyst poisoning. Laboratory experiments with other batches of ethyl acetate confirmed this hypothesis. It is worth mentioning that the impure ethyl acetate was approved according to the actual specification. After the hydrogenolysis was completed and the catalyst filtered off, the mixture was

treated with aqueous sodium sulfide in order to remove residual palladium.[15] A number of salt forms were screened in order to find a salt with good water solubility. The hemisulfate of lagociclovir valactate displayed a satisfactory water solubility of 9.8% w/v at room temperature. The mixture containing **1** as the acetate was treated with sulfuric acid in 2-propanol to give **1** as the hemisulfate salt in 73% yield from **4**. Analysis of the final product revealed an assay typically around 97% with water and 2-propanol as the major contaminants. Other impurities found were **2**, ranging from 0.2 to 1.2%, and guanine sulfate, typically 0.5%. Despite using palladium catalysis in the penultimate step[16] only 0−4 ppm palladium was detected when analyzed with AAS.

■ CONCLUSION

The highly water-soluble drug candidate lagociclovir valactate (**1**) was synthesized in five steps in an overall yield of 23%. The key N-glycosylation step resulted in a mixture of α- and β-anomers which were separated by column chromatography. Furthermore a problematic deprotection of the penultimate Cbz carbamate by hydrogenolysis was carried out. The synthesis, performed at kilogram scale, gave a material that fulfilled all regulatory requirements.

■ EXPERIMENTAL SECTION

General. HPLC analyses were performed using a YMC ODS-A, 5 μ, 250 mm × 4.6 mm, 120 Å equipped with an SB-C18 guard PAK. Elution conditions were employed with 20% acetonitrile in aqueous ammonium acetate (3 mM). The flow rate was 1.0 mL/min, and UV detection was at 220 nm for **1** and 254 nm for **2** and **5**. GC-analyses were performed using a J&W DB WAX, Bodman part # 123-7033, 0.5 μm film thickness, 0.32 mm i.d., 30 m length. Inlet temperature/detector temperature: 200/250 °C. Temperature gradient: 40 °C isothermal for 5 min and then ramped to 200 °C at profile 50 °C/min and held at 200 °C for 10 min. Optical rotations were measured with a Perkin-Elmer 241. NMR spectra were recorded at 300.14 MHz (proton) and 75.47 MHz (carbon) respectively. Thin layer chromatography was performed on Merck precoated TLC plates, which were visualized with concentrated H_2SO_4 followed by heating. Solvents and reagents were obtained from commercial sources and were used as such without any further purification. All reactors used were standard multipurpose equipment, either glass-lined or stainless steel. All reactions in pilot-plant scale were for safety reasons routinely carried out under an atmosphere of nitrogen.

2-Acetamido-6-chloropurine (3). In a stainless steel reactor charged with acetic anhydride (168 kg, 1645 mol) was added, under stirring, 2-amino-6-chloropurine (8.0 kg, 35.4 mol). The mixture was heated to 135 °C, at which point a mixture of acetic anhydride (5.5 kg, 48.6 mol) and phosphoric acid (85%, 34 g, 0.29 mol) was added. The mixture was refluxed for 75 min and then cooled to 30 °C. A 140−150 L volume of acetic acid anhydride was distilled off under reduced pressure (55−65 °C at 15−20 mbar). To the thick slurry was added methanol (480 L), and the mixture was stirred for 14 h at 20−25 °C. Ammonia (25%, 83 L) was added at such a rate that the temperature did not exceed 43 °C. The mixture was cooled and stirred for 6 h at 22−26 °C. The volume in the reactor was reduced via distillation at reduced pressure (15−20 mbar and not over 45 °C) until less than 130 L remained. After cooling to 20 °C the mixture was centrifuged, and the residue was washed with water (15 L). The moist material (12.2 kg) was charged to a mixture consisting of methanol (480 L) and ammonia (25%, 83 L). The mixture was heated to 35 °C during 1 h and then cooled to 20 °C. The mixture was transferred to another reactor via a cartridge filter after which activated charcoal (Filtrasorb 400, 0.8 kg) was added. After stirring for 1 h the mixture was filtered and the volume was reduced via distillation at reduced pressure (15−20 mbar and not over 45 °C) until less than 130 L remained.

The mixture was cooled to 20 °C. Centrifugation followed by washing with water (15 L) and drying at reduced pressure (8 mbar) at 50 °C gave the title compound (6.7 kg, 89%) as a white solid: mp >300 °C; IR 3161 (broad), 1724, 1578, 1491, 1380 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.79 (s, 1H), 8.53 (s, 1H), 2.19 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 168.4, 154.1, 151.9, 148.4, 145.0, 126.7, 24.4.

9-(5-Pivaloyl-3-fluoro-2,3-dideoxy-β-D-ribofuranosyl)-2-acetamido-6-chloropurine (5). In a glass-lined reactor charged with 1,4-dioxane (28.3 L) were added under stirring **3** (1.9 kg, 9.0 mol), ammonium sulfate (20 g, 0.15 mol, finely grounded), and 1,1,1,3,3,3-hexamethyldisilazane (1.32 kg, 8.2 mol). The mixture was heated gently to 96−99 °C and kept at reflux for 3 h (CAUTION! foaming). 1,4-Dioxane (9 L) was distilled off after which the mixture was cooled to 22−25 °C. To the mixture was added diisopropyl ether (19 L) and **6** (1.0 kg, 4.3 mol) followed by slow addition of trimethylsilyl trifluoromethanesulfonate (1.0 kg, 4.5 mol). After stirring for 20 h at 20 °C, a mixture of methanol (0.8 L) and triethylamine (0.8 L) was added at such a rate that the temperature did not exceed 25 °C. The mixture was cooled to 15 °C and then filtered through a glass-sintered funnel. The filtrate was concentrated to a thick oil at reduced pressure (10 mbar) and room temperature. Ethyl acetate (20 L) was added, and the resulting solution was washed with aqueous acetic acid (10%, 8 L) and aqueous potassium carbonate (10%, 8 L). Silica gel 60 (0.035−0.070 mm) (3 kg) was added to the organic phase, and the mixture was concentrated to dryness in an evaporator. The residue was purified with chromatography (silica gel 60, *n*-hexane−ethyl acetate, 2:3) which gave 0.728 kg (41%) of the pure β-anomer as white crystals: Mp >300 °C; $[\alpha]_D^{21}$ = +10.9 (*c* 2.3, $CDCl_3$.); R_f 0.20 (*n*-heptane−EtOAc 40:60); IR 3166 broad, 1725, 1580, 1429, 1383, 1229 cm^{-1}; ^1H NMR ($CDCl_3$) 8.37 (dd, J_1 = 8.2 Hz, J_2 = 6.1 Hz, 1H), 8.15 (s, 1H), 5.36 (dd, J_1 = 53.4 Hz, J_2 = 5.0 Hz, 1H), 4.53 (dt, J_1 = 24.0 Hz, J_2 = 5.5 Hz, 1H), 4.49−4.32 (m, 2H), 3.16−2.79 (m, 2H), 2.48 (s, 3H), 1.27 (d, *J* = 2.0 Hz, 1H), 1.21 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 178.1, 169.5, 151.8, 151.8, 151.6, 142.9, 128.8, 92.3 (d, *J* = 179 Hz), 85.4, 82.9 (d, *J* = 25 Hz), 62.9 (d, *J* = 10 Hz), 38.8, 37.5 (d, *J* = 21 Hz), 27.1, 25.1.

2,3′-Dideoxy-3′-fluoroguanosine (2). In a glass-lined reactor charged with water (107 L) was added sodium hydroxide (1.1 kg, 27.5 mol), and the mixture was stirred for 15 min. 2-Mercaptoethanol (1.2 kg, 15.4 mol) and **5** (2.184 kg, 5.28 mol) were added, and the mixture was heated to reflux. After 1.5 h at reflux, the mixture was cooled to 40−45 °C and acetic acid (1.7 kg, 28.3 mol) was added slowly over 1 h. The mixture was cooled to 0−4 °C and stirred at this temperature for 2 h. The crude product was isolated by filtration. Washing of the filtrate with cold (0−4 °C) water (20 L) and cold (0−4 °C) ethanol (5 L) followed by drying at reduced pressure (20 mbar) at 45−55 °C gave the title compound as white crystals (1.42 kg 100%): Mp 242 °C (dec.); $[\alpha]_D^{21}$ = −38.1 (*c* 0.53, DMF); IR 3166 (broad), 1726, 1636, 1596, 1543, 1487, 1401, 1056 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.69 (s, 1H), 7.95 (s, 1H), 6.49 (s, 2H),

6.14 (dd, J_1 = 5.6 Hz, J_2 = 9.2 Hz, 1H), 5.38 (dd, J_1 = 3.9 Hz, J_2 = 46.3 Hz, 1H), 5.16 (t, J = 5.4, 1H), 4.16 (dt, J_1 = 4.7 Hz, J_2 = 26.9 Hz, 1H), 3.56 (m, 2H), 2.92−2.53 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 161.9, 158.9, 156.2, 140.5, 121.9, 99.0 (d, J = 173 Hz), 90.2 (J = 22 Hz), 87.8, 66.1 (J = 11 Hz), 41.9 (J = 20 Hz).

(*S*)-(+)-2-(*N*-Cbz-L-valyloxy)propionic acid (7). In a glass-lined reactor charged with ethyl acetate (90 L) was added **7** as the dicyclohexylammonium salt[12] (6.0 kg, 11.9 mol) with stirring. Hydrochloric acid in diethyl ether (1.0 M, 12.9 L, 12.9 mol) was added during 30 min. The mixture was passed through a filter, which was washed with ethyl acetate (42 kg). The solution was concentrated by distillation under reduced pressure (20 mbar). Approximately 130 L were distilled off, and the remaining thick oil was used directly in the next step.

2′,3′-Dideoxy-3′-fluoro-5′-*O*-[(*S*)-(+)-2-(*N*-Cbz-L-valyloxy)-propionyl]guanosine (4). Compound **7** was dissolved in DMF (170 L) and transferred to a glass-lined reactor. To the reactor were added **2** (2.5 kg, 9.3 mol), 1-hydroxybenzotriazole (1.5 kg, 11.1 mol), 4-(dimethyl)aminopyridine (0.23 kg, 1.9 mol), and DMF (293 L) with stirring. DMF (230 L) was distilled off at reduced pressure (50−60°, 20 mbar) after which the mixture was cooled to 25−28 °C. *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC) (1.7 kg, 8.9 mol) was added, and the mixture was stirred for 5 h at 22−25 °C. Another portion of EDC (1.1 kg, 5.7 mol) was added, and stirring was continued for 14 h at 22−25 °C. Finally a small portion EDC (0.2 kg, 1.0 mol) was added, the mixture was heated to 42−46 °C and kept at this temperature for 1 h. The progress of the reaction was monitored with HPLC. DMF (227 L) was distilled off under reduced pressure (50−60 °C, 20 mbar) until a thick oil remained. Ethyl acetate (140 L) and water (60 L) were added, and the mixture was stirred for 15 min at ambient temperature. After phase separation the aqueous phase was extracted with ethyl acetate (90 L). The combined organic phases were washed with saturated aqueous sodium bicarbonate (2 × 74 L), water (15 L), 5% aqueous acetic acid (2 × 74 L), and again with water (15 L). Ethyl acetate was distilled off under reduced pressure (33−35 °C jacket temperature, 20 mbar) until a thick oil remained. Toluene (15 kg) was added to the oil and then distilled off under vacuum (40−45 °C jacket temperature, 20 mbar). To the remaining slurry was added ethanol (70 kg), and the mixture was heated to 75−78 °C and kept at this temperature for 10 min. Ethanol (50 L) was distilled off under reduced pressure (30−35 °C jacket temperature, 20 mbar), after which the mixture was cooled to 30−33 °C and diethyl ether (60 kg) was added. The mixture was cooled during 2 h to 0−4 °C and kept at this temperature for another 2 h. The resulting precipitate was isolated on a filter and washed with diethyl ether (10 kg). The moist material was mixed with diethyl ether (110 kg), stirred for 2 h, and isolated via filtration. This procedure was repeated one more time with 110 L diethyl ether and one time with 78 L of diethyl ether. After final filtration the residue was dried at 50 °C under reduced pressure (8 mbar) to give 4.56 kg (85%) of the title compound as a beige powder. $[\alpha]_D^{23}$ = −9.8 (*c* 0.60, EtOAc); mp 126−127 °C; IR 3150 (broad), 1752, 1702, 1633, 1595, 1517, 1090; ^{1}H NMR (DMSO-d_6) δ 7.92 (s, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.36 (m, 5H), 6.52 (s, 2H), 6.18 (dd, J_1 = 8.9 Hz, J_2 = 5.8 Hz,1H), 5.58−5.44 (m, 1H), 5.12 (m, 1H), 5.04 (s, 2H), 4.44−4.20, (m, 3H), 4.03 (m, 1H), 3.06−2.55 (m, 2H), 2.10 (m, 1H), 1.40 (d, J = 7.0 Hz, 3H), 0.92 (t, J = 7.0 Hz, 6H); ^{13}C NMR (DMSO-d_6) δ 171.2, 169.9, 156.6, 156.5, 153.7, 151.0, 135.3, 128.3, 127.8, 127.7, 116.9, 95.5, 82.7, 81.7, 81.5, 68.6, 65.5, 59.6, 29.7, 18.8, 17.6, 16.7.

2′,3′-Dideoxy-3′-fluoro-5-*O*-[(*S*)-(+)-2-(L-valyloxy)-propionyl]guanosine Hemisulfate (1), Lagociclovir Valactate. In a hydrogenation reactor charged with ethyl acetate (130 L kg) and acetic acid (45 L) was added **4** (4.53 kg, 7.9 mol). The mixture was warmed to 26−30 °C after which 10% palladium on charcoal (3.9 kg, 3.6 mol, 46 mol %) was added. The mixture was hydrogenated at 3 bar and 30 °C for 3 h. The progress of the reaction was checked with TLC and HPLC. The catalyst was filtered off, and the filter was rinsed with a 1:3 mixture of ethyl acetate and acetic acid (40 L). The combined organic phases were concentrated via distillation at reduced pressure (55−60 °C jacket temperature, 20 mbar) until 4−5 L remained. Water (4.4 L) was added to the oil and stirred at 22−25 °C for 15 min. Aqueous sodium sulfide (50%, 0.5 kg) was added, and the mixture was then stirred for 5 min followed by 15 min without stirring. A suspension of charcoal (40 g) in water (100 mL) was added and stirred for 20 min. The mixture was filtered, and the filtrate was transferred to a glass-lined reactor to which 2-propanol (5.4 kg) was then added. Aqueous sulfuric acid (20%, 2.47 kg, 5.04 mol) was added until the pH was 2.2−2.3. 2-Propanol (14 L) was added over 15 min with stirring. After 30 min the pH was adjusted to 2.2−2.3 by the addition of aqueous sulfuric acid (150 g) after which the mixture was stirred for another 2.5 h. The product was isolated via filtration and then washed with a 3:1 mixture of 2-propanol and water (3.4 L) and finally with 2-propanol (9 L). Drying at 50 °C under reduced pressure (8 mbar) for 8 h gave the title compound as a white powder. Yield 3.1 kg (73%) as hemisulfate.

$[\alpha]_D^{21}$ = +0.77 (*c* 1.6, H_2O); IR 3164 (broad), 1742, 1687, 1636, 1598, 1532, 1485, 1402, 1056 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.92 (s, 1H), 6.62 (s, broad, 2H), 6.20 (q, J = 6.0 Hz, 1H), 5.42, (dd, J_1 = 53.5 Hz, J_2 = 3.8 Hz, 1H), 5.15 (q, J = 6.9 Hz, 1H), 4.42−4.25 (m, 3H), 3.08−2.85 (m, 1H), 2.19−2.08 (m, 1H), 1.44 (d, J = 7.0 Hz, 3H), 1.04 (d, J = 6.1 Hz, 1H), 0.96 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 169.7, 168.4, 156.8, 153.8, 151.1, 135.5, 116.9, 92.8 (d, J = 175 Hz), 82.7 (d, J = 10 Hz), 81.5 (d, J = 25 Hz), 69.5, 64.3, 57.8, 36.0 (d, J = 20 Hz), 29.1, 25.5, 17.6, 16.7.

AUTHOR INFORMATION

Corresponding Author

*E-mail: johan.wennerberg@swe.dupont.com.

ACKNOWLEDGMENT

We are grateful to Johan Eriksson-Bajtner for help with NMR experiments; to Anna Castensson for assistance with analyses; to Carl-Magnus Andersson for valuable comments on the manuscript, and to Hans Uvelius and Roger Johnsson for running the pilot plant.

REFERENCES

(1) Zhou, X.-X.; Johansson, N.-G.; Wähling, H. WO 99/09031, 1998.

(2) Harmenberg, J.; Larsson, T.; Böttiger, D.; Augustsson, E.; Mardh, G. Öberg, B. *Antivir. Rec.* **2002**, *53*(3), Abstract 150.

(3) Jacquard, A.-C.; Brunelle, M.-N.; Pichoud, C.; Durantel, D.; Carrouée-Durantel, S.; Trepo, C.; Zoulim, F. *Antimicrob. Agents Chemother.* **2006**, *50*, 955–961.

(4) Michalak, T. I.; Zhang, H.; Churchill, N. D.; Larsson, T.; Johansson, N.-G.; Öberg, B. *Antimicrob. Agents Chemother.* **2009**, *53* (9), 3803–3814.

(5) Zhang, H.; Öberg, B.; Harmenberg, J.; Vrang, L.; Rydegård, C.; Larsson, T.; Samuelsson, B. *42nd Intersci. Conf. Antimicrob. Agents Chemother.* **2002**, Abstract-1853.

(6) (a) Iwamoto, R. H; Acton, E. M; Goodman, L. *Nature* **1963**, *198*, 263. (b) Acton E. M.; Iwamoto, R. H. In *Synthetic Procedures in Nucleic Acid Chemistry*; Zorbach, W. W., Tipson, R. S., Eds.; Interscience Publishers: 1968; pp 25−27.

(7) Saischek, G.; Fuchs, F.; Dax, K.; Billiani, G. Eur. Pat. 450585 A2 1991.

(8) (a) Niedballa, U.; Vorbrüggen, H. *J. Org. Chem.* **1974**, *39*, 3654–3660. (b) Niedballa, U.; Vorbrüggen, H. *J. Org. Chem.* **1974**, *39*, 3660–3663. (c) Niedballa, U.; Vorbrüggen, H. *J. Org. Chem.* **1974**, *39*, 3664–3667. (d) Niedballa, U.; Vorbrüggen, H. *J. Org. Chem.* **1974**, *39*, 3668–3671. (e) Niedballa, U.; Vorbrüggen, H. *J. Org. Chem.* **1974**, *39*, 3672–3674. (f) Niedballa, U.; Vorbrüggen, H. *J. Org. Chem.* **1976**, *41*, 2084–2086. (g) Hofle, G.; Vorbrüggen, H. *Chem. Ber.* **1981**, *114*, 1256–1268. (h) Vorbrüggen, H., Niedballa, U. U.S. Patent 3,748,320, 1973.

(9) Frescos, J. N. *Nucleosides Nucleotides* **1989**, *8*, 549–555.

(10) Hubbard, A. J.; Jones, A. S.; Walker, R. T. *Nucleic Acid Res.* **1984**, *12*, 6827–6837.

(11) For examples, see: (a) Kazimierczuk, Z.; Cottam, H. B.; Revankar, G. R.; Robins, R. K. *J. Org. Chem.* **1984**, *106*, 6379–6382. (b) Reference 9. (c) Reference 10.

(12) Bhattacharya, A. K.; Ness, R. K.; Fletcher, H. G., Jr. *J. Org. Chem.* **1963**, *28*, 428–435.

(13) Kotra, P. L.; Xiang, Y.; Newton, M. G.; Schinazi, R. F.; Cheng, Y.-C.; Chu, C. K. *J. Med. Chem.* **1997**, *40*, 3635–3644.

(14) Vinogradova, E. I.; Fonina, L. A.; Sanasaryan, A. A.; Ryabova, I. D.; Ivanov, V. T. *Khimiya Prirodnykh Soedinenii.* **1974**, *10* (2), 233–240.

(15) For a review of methods for removal of palladium residues, see: Garrett, C. E.; Prasad, K. *Adv. Synth. Catal.* **2004**, *346*, 889–900.

(16) Rosso, R. W.; Lust, D. A.; Bernot, P. J.; Grosso, J. A.; Modi, S. P.; Rusowicz, A.; Sedergran, T. C.; Simpson, J. H.; Srivastava, S. K.; Humora, M. J.; Anderson, N. G. *Org. Process Res. Dev.* **1997**, *1*, 311–314 and references cited therein.