

A facile synthesis of potent antiherpes drug substance, Ganciclovir, 9-[(1,3-Dihydroxy-2-propoxy)methyl]guanine, using a new masked glycerol derivative[§]

V. V. N. K. V. Prasada Raju,*^a Vedantham Ravindra,^a Suchitra S. Kamath,^a Vijayavithal T. Mathad,^a Pramod K. Dubey,^b and Padi Pratap Reddy^a

^aDepartment of Research and Development, Integrated Product Development, Innovation Plaza, Dr. Reddy's Laboratories Ltd., Survey Nos. 42, 45, 46 & 54, Bachupally, Qutubullapur, R. R.

Dist-500 072, Andhra Pradesh, India

^bDepartment of Chemistry, Jawaharlal Nehru Technological University, Kukatpally, Hyderabad-500 072, Andhra Pradesh, India

E-mail: prasadvvnkv@drreddys.com

Abstract

A short and facile synthesis of an antiherpes drug substance, ganciclovir is developed using a new masked glycerol derivative as one of the key starting materials.

Keywords: Ganciclovir, acyclic nucleoside, antiviral, diacetylguanine, masked glycerol

Introduction

Ganciclovir **1** (Figure 1) is a guanine containing acyclic nucleoside drug (Cytovene, RxList) used to treat infections caused by herpes family viruses and cytomegalovirus.^{1,2} In view of its substantial commercial importance, several synthetic routes were developed for ganciclovir using guanine,^{3,4} acetylguanine,³ 2-amino-6-chloropurine,^{3,5} tetraacetylguanosine,^{6,7} and diacetylguanine **2** (Figure 1),⁸⁻¹¹ as the source of guanine moiety. Coupling of one of such guanine derivatives with an appropriately protected, activated glycerol derivative such as 1,3-diacetoxy-2-acetoxymethoxy propane or 1,3-dibenzyloxy-2-acetoxymethoxy propane is the commonly employed strategy to access ganciclovir.

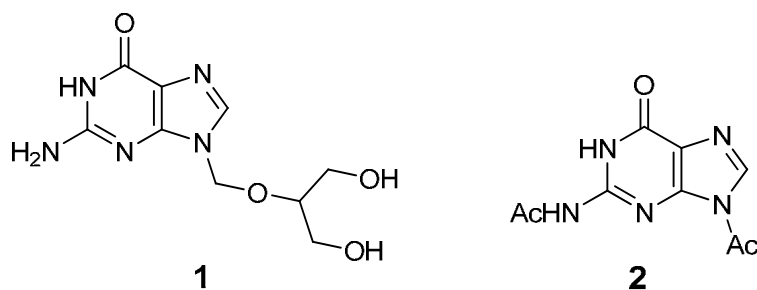
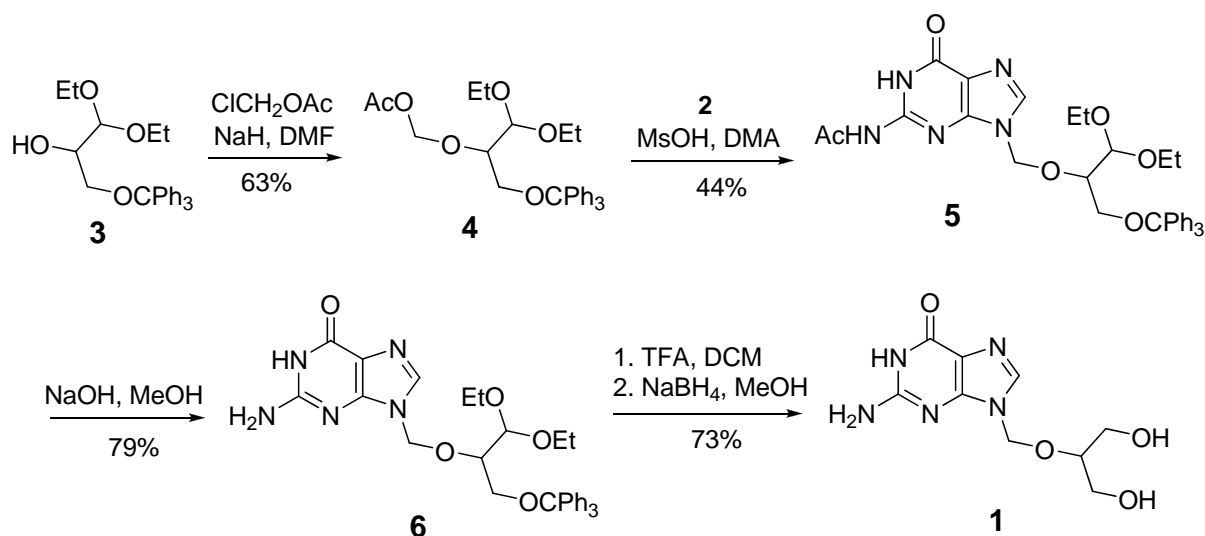


Figure 1. Ganciclovir and diacetylguanine.

Results and Discussion

In our current approach, a new, readily accessible masked glycerol derivative, 2-acetoxymethoxy-1,1-diethoxy-3-trityloxypropane **4** is used as a source of 1,3-dihydroxy-2-propoxymethyl moiety in the synthesis of ganciclovir (Scheme 1). Acetal and trityloxy functions of **4** can be readily transformed into the desired hydroxyls under mild conditions in the final stage of synthetic sequence.



Scheme 1. Synthesis of Ganciclovir.

In the reported processes for the introduction of acetoxymethyl moiety onto the secondary hydroxyl function of appropriate terminal protected glycerol derivatives, a two step protocol involving chloromethylation and subsequent nucleophilic displacement with acetoxy was practiced.^{8,12} We have developed a relatively simple and convenient one step process for functionalizing the secondary hydroxyl to furnish the desired intermediate **4**.

Selective tritylation of the commercially available glyceraldehyde diethyl acetal gave 1,1-diethoxy-3-trityloxypropan-2-ol (**3**).¹³ Reaction of **3** with chloromethyl acetate in the presence of sodium hydride in DMF provided the desired substrate **4** in good yields.

Among several reagent/ solvent combinations (Table 1), NaH/ DMF was proved to be an apt combination to facilitate the conversion of 2-propanol derivative **3** into the desired intermediate **4** (Entry 6, Table 1). The mode of addition of reagents had a tremendous effect on the yield of the reaction. The reaction proceeded with formation of impurities upon successive addition of NaH, **3** and chloromethyl acetate in DMF thereby resulting in low yield of **4**, the major impurity being the acetyl derivative of **3**. The yield drastically increased by first activation of **3** using NaH followed by dropwise addition of this activated **3** to chloromethyl acetate in DMF.

Table 1. Reagent/ solvent combinations for conversion of 2-propanol derivative **3** to **4**

Entry	Base	Solvent	Yield (%)
1	K ₂ CO ₃	Acetone	0
2	K ₂ CO ₃	DCM	0
3	K ₂ CO ₃ , NaI	Acetone	4
4	DMAP	DCM	0
5	KOH	DMF	9
6	NaH	DMF	63
7	NaH	Toluene	49
8	NaH	THF	52
9	NaH	DMSO	45

Such a one step chloromethylation of secondary hydroxyl function to get similar structural motif was hitherto be unknown in the literature.

Reaction of **4** with diacetylguanidine **2** was conducted in dimethylacetamide in the presence of methanesulfonic acid to give **5** (44%). The acetamido guanine derivative **5** could be smoothly transformed into its corresponding amino derivative **6** (79%) on alkaline hydrolysis in methanol. The preparation of **5** and **6** were done by following the similar procedure reported in literature.¹⁰ Concomitant deprotection of acetal and trityl functions of **6** using TFA in DCM and subsequent reduction of the aldehyde derivative using NaBH₄ in the same pot directly furnished ganciclovir **1** (73%). The formation of **1** (16% when calculated from **3**) was confirmed by comparison of analytical data with that of authentic compound reported in literature.⁸

Conclusions

In conclusion, readily accessible substrates, relatively mild reaction conditions and simple inexpensive deprotection operations render our approach to ganciclovir attractive. Further

application of this synthetic protocol in the synthesis of structurally similar and commercially important antiviral active pharmaceutical ingredients is under exploration.

Experimental Section

General. IR spectra were recorded in the solid state as a KBr dispersion using a Perkin-Elmer FT-IR spectrophotometer. ^1H NMR spectra were scanned in $\text{DMSO-}d_6$ on a Mercury Plus spectrometer with TMS as an internal standard. HR-MS spectra were obtained on Waters LCT Premier XE (Micro mass Oa-TOF) instrument. The solvents and reagents were used without any purification.

Preparation of 2-acetoxymethoxy-1,1-diethoxy-3-trityloxypropane (4). To a solution of NaH (144 mg, 6 mmol) in anhydrous DMF (25 mL) was added 1,1-diethoxy-3-trityloxypropan-2-ol **3**¹³ (4.06 g, 10 mmol) at room temperature and reaction mixture was stirred for 10 h under N_2 . This solution was added dropwise at regular intervals to a cooled solution of chloromethyl acetate (1.0 mL, 10 mmol) in DMF (25 mL) at 15-20 °C. The reaction mixture was stirred for 5-6 h, quenched with chilled water and extracted with diisopropyl ether. The ether layer was dried over sodium sulfate and concentrated under vacuum to give crude compound **4** as a residue, which was purified by column chromatography eluting with 10% MeOH in EtOAc; yield: 3 g (63%); IR (KBr): 3444, 3086, 3059, 2974, 2874, 1747, 1649, 1490, 1448, 1227, 1154, 1066, 1012, 947, 704 cm^{-1} ; ^1H NMR (400 MHz, $\text{Me}_2\text{SO-}d_6$): δ = 7.46-7.42 (m, 6H), 7.30-7.20 (m, 9H), 4.53 (d, J = 6.3 Hz, 1H), 4.29 (s, 2H), 3.81-3.77 (m, 1H), 3.60-3.54 (m, 2H), 3.33-3.29 (m, 2H), 3.23-3.18 (m, 2H), 2.01 (s, 3H), 1.00 (t, 3H), 0.86 (t, 3H); HRMS for $\text{C}_{29}\text{H}_{34}\text{O}_6$ $[\text{M}+\text{H}]^+$: m/z Calcd: 479.2699; Found: 479.2702.

Preparation of N^2 -acetyl-9-[(1,1-diethoxy-3-trityloxy-2-propoxy)methyl]guanine (5). To a solution of diacetylguanine **2** (1.41 g, 6 mmol) and 2-acetoxymethoxy-1,1-diethoxy-3-trityloxypropane **4** (2.9 g, 6 mmol) in dimethylacetamide (30 mL) was added methanesulfonic acid (0.1 mL, 1.2 mmol) at room temperature. The reaction mixture was heated at 75-80 °C for 20-21 h, cooled to room temperature and extracted with DCM. The DCM layer was dried over sodium sulfate and concentrated under vacuum to give crude compound **5**, which was purified by column chromatography eluting with 4% MeOH in CHCl_3 ; yield: 1.6 g (44%); IR (KBr): 3120, 3054, 2927, 2855, 1692, 1617, 1547, 1449, 1373, 1265, 1083, 1062, 896, 738 cm^{-1} ; ^1H NMR (400 MHz, $\text{Me}_2\text{SO-}d_6$): δ = 12.15 (s, 1H), 11.63 (s, 1H), 8.46 (s, 1H), 7.28-7.19 (m, 15H), 5.8 (s, 2H), 4.38 (d, J = 6.1 Hz, 1H), 4.03-3.99 (m, 1H), 3.57-3.37 (m, 4H), 2.93-2.89 (m, 2H), 2.16 (s, 3H), 0.86 (t, 3H), 0.83 (t, 3H); HRMS for $\text{C}_{34}\text{H}_{37}\text{N}_5\text{O}_6$ $[\text{M}+\text{H}]^+$: m/z Calcd: 612.2822; Found: 612.2835.

Preparation of 9-[(1,1-diethoxy-3-trityloxy-2-propoxy)methyl]guanine (6). A solution of compound **5** (1.83 g, 3 mmol) and NaOH (0.12 g, 3 mmol) in MeOH (15 mL) was stirred at 40-50 °C for 3-4 h. The reaction mixture was cooled to room temperature and extracted with EtOAc.

The organic extract was dried over sodium sulfate and concentrated under vacuum to give compound **6**; yield: 1.35 g (79%); IR (KBr): 3321, 3167, 3059, 3033, 2973, 2928, 1685, 1560, 1475, 1448, 1377, 1213, 1089 cm^{-1} ; ^1H NMR (400 MHz, $\text{Me}_2\text{SO}-d_6$): δ = 10.82 (s, 1H), 8.17 (s, 1H), 7.43-7.20 (m, 15H), 6.15 (s, 2H), 5.75 (s, 2H), 4.36 (d, J = 5.9 Hz, 1H), 4.01-3.98 (m, 1H), 3.54-3.43 (m, 4H), 2.94-2.88 (m, 2H), 1.01 (t, 3H), 0.86 (t, 3H); HRMS for $\text{C}_{32}\text{H}_{35}\text{N}_5\text{O}_5$ $[\text{M}+\text{H}]^+$: m/z Calcd: 570.2716; Found: 570.2728.

Preparation of ganciclovir (1). A mixture of compound **6** (569 mg, 1 mmol) and TFA (0.3 mL, 4 mmol) in DCM (10 mL) was stirred at room temperature for 4h. The solvent was stripped off under reduced pressure and MeOH (20 mL) was added to the residue and the solution was stirred at 10-15 °C. Sodium borohydride (45.6 mg, 1.2 mmol) was added in portions and the mixture was stirred for 2 h at 25 °C. The reaction mixture was poured into cold water, the solid obtained was filtered and recrystallized from MeOH to give ganciclovir as a white solid; yield: 186 mg (73%); mp 248-250 °C; IR (KBr): 3420, 3320, 3159, 3101, 2942, 2892, 1687, 1658, 1491, 1475, 1367, 1064, 1045 cm^{-1} ; ^1H NMR (400 MHz, $\text{Me}_2\text{SO}-d_6$): 10.62 (s, 1 H), 7.796 (s, 1 H), 6.47 (s, 2 H), 5.43 (s, 2 H), 4.62 (t, 2 H), 3.53 (m, 1 H), 3.30-3.52 (m, 4 H).

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