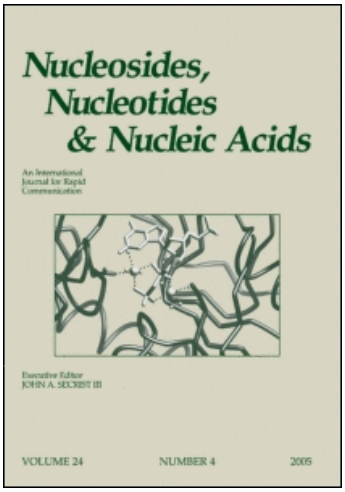

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V. Bhat[a]; B. C. Ugarkar[ab]; K. Grirara[a]; E. Stocker[a]; P. A. Domenico[a]; V. A. Sayeed[a]; N. Kosora[a]
[a] Pharra-Eco Laboratories Inc., Simi Valley, CA [b] Gensia pharmaceuticals, Inc., San Diego, CA

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AN IMPROVED SYNTHESIS OF 2',3'-DIDEOXYCYTIDINE

V. Bhat*, B.G. Ugarkar*†, K. Grimm, E. Stocker,
P.A. Domenico, V.A. Sayeed and N. Kosora

Pharm-Eco Laboratories Inc.
2355 Chain Drive, Simi Valley, CA 93065

Abstract: A convenient synthesis of 2',3'-dideoxycytidine (ddC, **6**) from 2'-deoxycytidine (**1**) has been achieved employing a base-catalyzed elimination of 3'-O-methanesulfonyl group as the key step.

2',3'-Dideoxynucleosides have shown remarkable inhibitory effect in vitro against human immunodeficiency virus (HIV) indicating their potential use in Acquired Immune Deficiency Syndrome (AIDS) chemotherapy.[1,2] Of these dideoxynucleosides, 2',3'-dideoxycytidine (ddC, **6**) is reported[2] to be the most potent member of the group which has resulted in its being evaluated clinically. The large quantities of **6** required for the clinical trials warranted the design of a new synthesis to produce it efficiently as well as economically on a large scale.

Several syntheses of 2',3'-dideoxycytidine are documented in the literature, the very first one by Horwitz and coworkers[3] and more recently by others.[4-9] However, all these syntheses are limited to small scale preparations, except for a recent report by Kaskar and Markovac.[9] Even this synthesis, though an improvement over the previous ones, suffers from its lengthy nature and less than attractive overall yield (23%). Herein, we describe a concise and economically viable procedure for the synthesis of 2',3'-dideoxycytidine starting from 2'-deoxycytidine (**1**) (Scheme 1).

Our synthesis of 2',3'-dideoxycytidine begins with selective benzoylation of **1**[10] using benzoic anhydride in DMF to give N^4-benzoyl-2'-deoxycytidine (**2**) in 83% yield. Protection of the 5'-OH and 3'-OH groups in **2** were achieved by treating it with trimethylacetyl chloride and methanesulfonyl chloride

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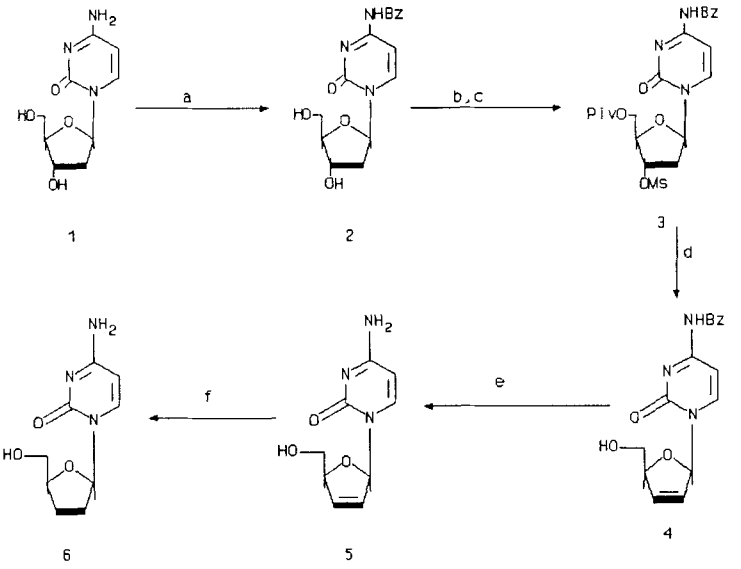
† Current address: Gensia Pharmaceuticals, Inc., 11075 Roselle St., San Diego, CA 92121-1207

SCHEME 1



a. DMF/Bz_2O; b. Pyridine,PivCl, -10°C; c. MsCl; d. NaOMe/DMF, -10°C;
e. Amberlite IRA-400(OH^-); f. H_2, $Pd/BaCO_3$ (5%)

Bz=C_6H_5CO; Ms=CH_3SO_2; Piv=$(CH_3)_3C$-CO-

respectively, to afford N^4-benzoyl-3'-O-methanesulfonyl-5'-O-trimethylacetyl-2'-deoxycytidine (3) in 72% isolated yield. Treatment of 3 with anhydrous sodium methoxide in DMF resulted in the base-catalyzed elimination reaction to produce N^4-benzoyl-2',3'-didehydro-2',3'-dideoxycytidine (4) in almost quantitative yield. A similar base-catalyzed elimination reaction in the case of 2'-deoxyadenosine derivative has been reported by Robins and coworkers.[11] Deblocking of the benzoyl group from 4 was accomplished by stirring it with Amberlite IRA 400 (OH^-) resin in methanol and the olefin thus obtained without isolation was subjected to hydrogenation in methanol-water employing 5% palladium on barium carbonate catalyst to afford the title compound in excellent yield.

Thus, we have outlined here a short (5 steps) synthesis of 2',3'-dideoxycytidine starting from 2'-deoxycytidine in an overall yield of 45%. It is also worth mentioning that the entire process could be scaled up to obtain multi-kilogram quantities of 6, thus making this procedure highly advantageous over the existing ones.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H NMR spectra were recorded in (methyl

sulfoxide)-d_6 on a Varian EM 390 spectrometer using tetramethylsilane as internal standard. Infrared spectra were recorded on a Beckman Model 25 spectrometer. Elemental analyses were performed by MHW Laboratories, Phoenix, Arizona. Thin-layer chromatography was run on silica gel GF plates (Analtech, Newark, Del.), where the products were visualized by UV light as well as 10% H_2SO_4 in MeOH spray followed by heating. Evaporations were carried out under reduced pressure with bath temperature below 40 °C.

N^4-Benzoyl-2'-deoxycytidine (2). A mixture of 2'-deoxycytidine (1) (3.3 Kg, 14.52 mol), benzoic anhydride (3.40 Kg, 15.04 mol) and DMF (33 L) was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the syrupy residue was triturated with absolute ether (16 L). The resulting white crystalline product was collected by filtration under suction, washed with ether (3 x 8 L) and air-dried. Further drying in a vacuum oven at 40 °C for 48 h gave 3.99 Kg (83%) of 2, mp 223-225 °C (dec.) (lit.[12] mp 230 °C (dec.)).

N^4-Benzoyl-3'-O-methanesulfonyl-5'-O-trimethylacetyl-2'-deoxycytidine (3). A solution of 2 (2.0 Kg, 6.04 mol) in anhydrous pyridine (20 L) was cooled to -5 °C and to this cold solution was added trimethylacetyl chloride (946.8 g, 7.85 mol) slowly in a dropwise fashion over a 6 h period, care being taken to maintain the reaction temperature around -5 °C. After the addition was complete, the reaction mixture was allowed to stir overnight between -5 ° and 0 °C and then methanesulfonyl chloride (1.38 Kg, 12.08 mol) was added slowly at this temperature. After stirring the reaction for another 6 h, it was then poured into ice-cold water (180 L), stirred vigorously for 1 h and allowed to stand at room temperature overnight. The aqueous layer was removed by decantation and the gummy white residue was triturated with hot 95% ethanol (16 L) resulting in the formation of a white precipitate. The product was collected by filtration, washed with cold 95% ethanol (3 L) and dried to afford 2.14 Kg (72%) of the title compound 3, mp 144-146 °C (dec.). An analytically pure sample of 3 was obtained by recrystallization of a small sample from 90% ethanol, mp 149-150 °C (dec.). ^{1}H NMR (DMSO-d_6) δ 1.23 (9H, s, $(CH_3)_3CCO$), 2.24 (2H, m, 2'-H), 3.12 (3H, s, $MeSO_2$), 4.37 (2H, d, J=4.5 Hz, 5'-H), 4.61 (1H, m, 4'-H), 5.27 (1H, m, 3'-H), 6.22 (1H, m, 1'-H), 7.52 (1H, d, J=7.5 Hz, 5-H), 7.56 (3H, m, aromatic), 7.80 (2H, m, aromatic), 8.01 (1H, d, J=7.5 Hz, 6-H), 9.00 (1H, br s, NH). UV λ_{max} (MeOH) 258 nm (ϵ 24,300), 300 (10,380).

Anal. Calcd. for $C_{22}H_{27}N_3O_8S$: C, 53.54; H, 5.51; N, 8.51; O, 25.93; S, 6.49. Found: C, 53.55; H, 5.67; N, 8.55; O, 26.14; S, 6.61.

N^4-Benzoyl-2',3'-didehydro-2',3'-dideoxycytidine (4). To a suspension of anhydrous sodium methoxide (353.0 g, 6.66 mol) in DMF (4 L) was added slowly with stirring, a solution of 3 (1.096 Kg, 2.22 mol) in DMF (4 L) at -10 °C. After stirring between -10 ° → -5 °C for 1 h, an additional 20 g (0.37 mol) of sodium methoxide was added and stirred for another hour. The pH of the reaction mixture was adjusted to 7 by the addition of glacial acetic acid (225 mL), the solvents were evaporated under reduced pressure and the residue obtained was stirred with cold water (5 L) and allowed to stand at 5 °C for 16 h. The crystalline product (4) separated was filtered, washed with ice-cold water and dried to give 652.0 g (92%) of the crude material. An analytically pure sample of 4 was obtained by recrystallization from hot ethanol, mp >265 °C; ^{1}H NMR (DMSO-d_6) δ 3.70 (2H, m, 5'-H), 4.95 (1H, m, 4'-H), 5.13 (1H, t, J= 5.4 Hz, OH), 6.10 (1H, br d, J=6 Hz, 2'-H), 6.50 (1H, br d, J=6 Hz, 3'-H), 7.00 (1H, m, 1'-H), 7.37 (1H, d, J=7.5 Hz, 5-H), 7.53-7.80 (3H, m, aromatic), 8.12 (2H, m, aromatic), 8.38 (1H, d, J=7.5 Hz, 6-H), 11.37 (1H, br s, NH). UV λ_{max} (MeOH) 257 nm (ϵ 24,500), 301 (9700).

Anal. Calcd. for $C_{16}H_{15}N_3O_4$: C, 61.33; H, 4.82; N, 13.41; O, 20.43. Found: C, 61.13; H, 4.97; N, 13.58; O, 20.19.

2',3'-Dideoxycytidine (6). To a suspension of 4 (650.0 g, 2.07 mol) in methanol (12 L) was added Amberlite IRA-400 (OH^-) resin (1.5 Kg) and stirred for 15 h at room temperature. The resin was removed by filtration, washed with methanol (11 L) and water (8 L). The combined filtrates were concentrated to a volume of ≈15 L and this solution containing the olefin (5) was subjected to hydrogenation using 150 g of 5% Pd/$BaCO_3$ catalyst under 20 psi of H_2 pressure. After 2 h, the hydrogenation was stopped, the catalyst was removed by filtration through a filter-pad and the filtrate was evaporated to dryness to obtain 334 g (76%) of a white crystalline material, mp 215 °C. This crude product was recrystallized from ethanol-water (9:1, 3.5 L) to give 272 g (62%) of analytically pure 2',3'-dideoxycytidine, mp 216-218 °C (lit.[3] 215-217 °C); ^{1}H NMR (DMSO-d_6) δ 1.56-2.56 (4H, m, 2'- and 3'-H), 3.63 (2H, m, 4'-H), 4.07 (1H, m, 4'-H), 4.98 (1H, m, OH), 5.76 (1H, d, J=7.5 Hz, 5-H), 5.98 (1H, m, 1'-H), 7.13 (2H, s, NH_2), 7.91 (1H, d, J=7.5 Hz, 6-H). UV (0.1 N HCl) λmax 280 nm (ϵ 13,150).

Anal. Calcd. for $C_9H_{13}N_3O_3$: C, 51.18; H, 6.20; N, 19.89; O, 22.73. Found: C, 51.35; H, 5.99; N, 19.63; O, 22.54.

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