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Synthesis of 2',3'-Dideoxyisoguanosine from Guanosine

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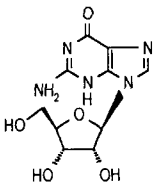
2',3'-dideoxyisoguanosine was synthesized from guanosine *via* intermediate 6-[(4-methylphenyl)thio]-2-oxo-9-(2',3',5'-tri-O-acetyl-β-D-ribofuranosyl)-2,3-dihydropurine (**4**). The 2-oxo, 6-amino and 5'-hydroxy triprotected isoguanosine derivative was utilized to reduce high polarity and promote poor solubility of intermediates. The protecting groups for oxo and 6-amino were easily removed in reduction of olefin in ribose without additional reaction steps. 2',3'-Vicinal diol in ribose sugar moiety was transformed to olefin with Bu_3SnH by radical reaction *via* bisxanthate. Removing 5'-O-TBDMS protecting group gave final product, 2',3'-dideoxyisoguanosine (**12**) in a 10 % overall yield.

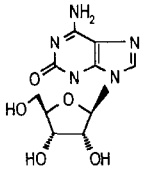
Key words: 2',3'-Dideoxyisoguanosine, Guanosine, Isoquanosine, Antiviral agent

INTRODUCTION

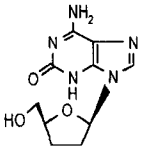
A HIV(Human Immunodeficiency Virus) requires specific enzyme, reverse transcriptase, for transcription from viral RNA to DNA in early stage of duplication. (Cheng *et al.*, 1987) It has been reported that several 2',3'-dideoxy nucleoside derivatives are very effective as an inhibitor of reverse transcription (Ono *et al.* 1986). AZT (3'-azido-3'-deoxythymidine), ddI (2',3'-di-deoxy inosine) and ddC (2',3'-dideoxycytidine) (Manchand *et al.*, 1990) acquired admission as an anti-AIDS drug (Herdewijn *et al.*, 1992) from FDA (Food and Drug Admini-stration). Furthermore, other dideoxy-nucleosides such like d4T (2',3'-didehydro-3'-deoxythym-idine) (Huryn *et al.*, 1992; Sekine *et al.*, 1990) and AZddU (3'-azido-2',3'-dideoxyuridine) are in progress of preliminary clinical test (Mansuri *et al.*, 1989; Matthes *et al.*, 1987). Isoguanosine is a naturally occuring isomer of guanosine which has a switching structure of 2-amino group and 6-hydroxy group in purine base of guanosine, and was first isolated in 1932 from *Croton tiglium L.* by Chebuliez and Bernhard. Isoguanosine has been reported to possess various biological activity in mammalian as hypertension, bradycardia, IMP pyrophosphorylation inhibition, inhibition of glutamic acid dehy-drogenase and anticancer activity (Kim *et al.*, 1994; Lee *et al.*, 1994) etc. In this paper, since isoguanosine is a unique type of nucleoside having various biological activity, we here synthesized the 2',3'-dideoxy-isoguanosine (Prisbe *et al.*, 1985) *via* the valuable intermediate 6-[(4-methylphenyl) thio]-2-oxo-9-(2',3',5'-tri-O-acetyl-β-D-ribo furanosyl)-2,3-dihydropurine (**4**). The whole steps of systhesizing 2',3'-dideoxyisoguanosine from guanosine were represented in Scheme 1. The tests of 2',3'-dideoxy isoguanosine for antitumor, antiretroviral and other bio-logical activity is now in process and the results will be discussed in later.



Guanosine



Isoguanosine



2',3'-Dideoxyisoguanosine

MATERIALS AND METHODS

General

Guanosine was purchased from Sigma Chemical Co. and all other reagents from Aldrich Chemical Co.. Melting points were determined on an Electrothermal apparatus and are uncorrected. NMR spectra were obtained on a Jeol 300 FT-NMR spectrometer with TMS as the chemical shift standard. Mass spectra were obtained from a VG 70-250S spectrometer. Thin layer

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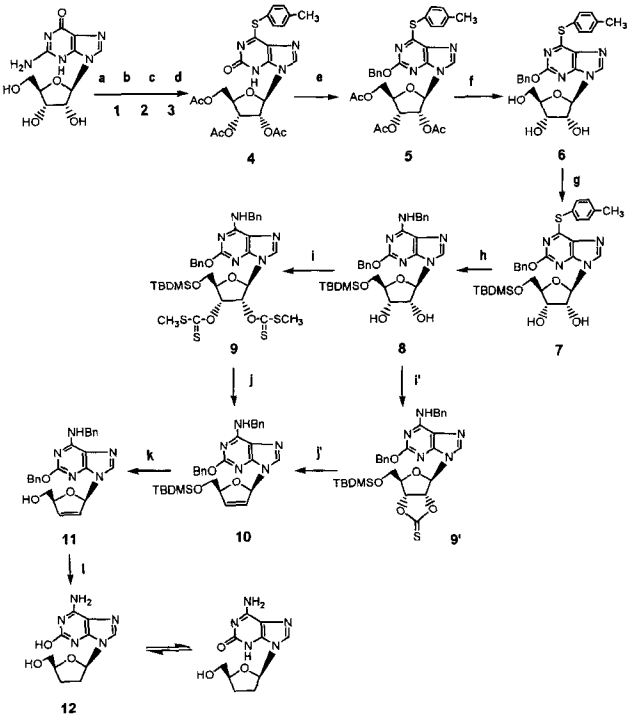
chromatography (TLC) was performed on Merck silica gel 60 F_{254} precoated sheets and column chromatography on Merck silica gel 60.

6-[(4-Methylphenyl)thio]-2-oxo-9-(2',3',5'-tri-O-acetyl-β-D-ribofuranosyl)-2,3-dihydropurine(4) [$C_{23}H_{24}N_4O_8S$:Fw =516.1]

Compound **4** was synthesized *via* 2',3',5'-tri-*O*-acetylguanosine (**1**),2-amino-6-chloro-9-(2',3',5'-tri-*O*-β-D-ribofuranosyl) purine (**2**), 2-amino-6-[(4-methylphenyl) thio]-9-(2',3',5'-tri-*O*-acetyl-β-D-ribofuranosyl)purine (**3**) from guanosine as a starting material using K. J. Divakar's method.

2-O-Benzyl-6[(4-methylphenyl)thio]-9-(2',3',5'-tri-*O*-acetyl-β-D-ribofuranosyl)purine(5) [$C_{30}H_{30}N_4O_8S$: Fw=606.1]

To a solution of compound **4** (5 g, 9.7 mmol), K_2CO_3 (2 g, 14.55 mmol) and tetraethylammonium iodide (0.03 g, 0.43 mmol) in DMSO (75 ml), BnBr (0.92 ml, 12.32 mmol) was added dropwise and stirred at room temperature for 18 h. The reaction mixture was diluted with diethyl ether (150 ml) and washed with cold water (75 ml × 3). Organic layer was separated with separation funnel and dried ($MgSO_4$). After evaporation, chromatography on a silicagel column with $CHCl_3$-MeOH (8 : 2) gave **5** (5.17 g, 88 %). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.03 (1H, s, 8-H), 7.5-7.1 (4H, dd, -S-$C_6\underline{H}_4$-CH_3), 7.35-7.15 (5 H, m, -O-CH_2-$C_6\underline{H}_5$), 6.21 (1H, d, 1'-H), 5.82 (1H, t, 2'-H), 5.57 (1H, t, 3'-H), 5.2-5.1 (2H, d, -O-$C\underline{H}_2$-C_6H_5), 4.42-4.24 (3H, m, 4',5'-H), 2.43 (3H, s, -S-$C\underline{H}_3$), 2.07-2.02 (9H, m, CH_3CO-).



a) DMF, acetic acid, pyridine, 70°C, 3h. b) $POCl_3$, *N,N*-dimethylaniline, acetonitrile, 100°C, 10 min. c) *p*-thiocresol, Et_3N, DMF, 100°C, 1.5h. d) $NaNO_2$, acetic acid: H_2O (1:1,v/v), 50°C, 2h. e) tetraethylammonium iodide, BnBr, K_2CO_3, DMSO, RT, 18h. f) NaOMe, MeOH, RT, 15min. g) *tert*-butyldimethylsilyl chloride, imidazole, DMF, 80°C, 2h. h) Benzylamine: EtOH (1:1,v/v), 80°C, 24h. i) CS_2, DMF, 5N NaOH, RT, 30 min, then CH_3I, RT, 1h. i') 1,1-thiocarbonyldiimidazole, DMF, 80°C, 2h. j) tributyltin hydride, AIBN, toluene, 80°C-reflux, 2h. j') 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine, acetonitrile, RT, 8h. k) 1N tetra-*n*-butylammonium iodide, THF, 0°C, 1h. l) Pd/C, MeOH, H_2(45 psi), 50°C, 24h.

Scheme 1. Synthesis of 2',3'-dideoxyisoguanosine

2-O-Benzyl-6-[(4-methylphenyl)thio]-9-(β-D-ribofuranosyl) purine (6) [$C_{24}H_{33}N_4O_8S$: Fw=528.1]

A mixture of compound **5** (5.17 g, 8.53 mmol) and NaOMe (1.76 g, 32.45 mmol) in CH_3OH (40 ml) was stirred at room temperature for 15 min. The reaction mixture was diluted with CH_3OH (100 ml) and titrated to pH 7-8 using Dowex resin. After filtering Dowex resin, rapid crystallization from acetonitrile gave compound **6** (4.14 g, 92 %). : ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.79 (1H, s, 8-H), 7.45 -7.05 (4H, dd, -S-$C_6\underline{H}_4$-CH_3), 7.28-7.14 (5H, m, -O-CH_2-$C_6\underline{H}_5$), 5.89 (1H, d, 1'-H), 5.03 (1 H, d, -O-$C\underline{H}_2$-C_6H_5), 4.79 (1H ,d, -O-$C\underline{H}$-C_6H_5), 4.52 (1 H, t, 2'-H), 4.29 (1H, t, 3'-H), 3.98-3.94 (1H, m, 4'-H), 3.75-3.39 (2H, m, m, 5'-H), 2.35 (3H, s, -S-C_6H_4-$C\underline{H}_3$).

2-O-Benzyl-6-amino-9-[5'-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]purine (7) [$C_{30}H_{38}N_4O_5SSi$: Fw=594.19]

To a suspension of compound **6** (4.47 g, 8.46 mmol) and imidazole (0.92 g, 13.5 mmol) in dry DMF (68 ml) was added *tert*-butyldimethylsilyl chloride (3.06 g, 20.3 mmol). The mixture was stirred at room temperature for 20 h. The reaction mixture was evaporated *in vacuo*. The oily residue was diluted with ethyl acetate and filtered. After evaporation of filtrate, the residue was chromatographed on a silicagel column using EtOAc-*n*-Hexane (1:1) gave compound **7** (3.67 g, 73 %). : ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.1 (1H, s, 8-H), 7.53-7.1 (4H, dd, -S-$C_6\underline{H}_4$- CH_3), 7.25-7.26 (5H, m, -O-CH_2-$C_6\underline{H}_5$), 5.95 (1H, d, 1'-H), 5.1 (2H, d, -O-$C\underline{H}_2$-C_6H_5), 5.08 (1H, t, 2'-H), 4.5 (1H, t, 3'-H), 4.4-4.2 (1H, m, 4'-H), 3.87-3.82 (2H, m, 5'-H), 2.4 (3H, s, -S-C_6H_4-$C\underline{H}_3$), 0.9 (9H, s, *tert*-Butyl).

2-O-Benzyl-6-benzylamino-9-[5'-(tert-butyldimethylsilyl)-β-D-ribofuranosyl]purine(8)[$C_{30}H_{39}N_5O_5Si$: Fw=577.14]

To a 250 ml high-pressure ensuring vessel, compound **7** (3 g, 5.04 mmol) and EtOH-Benzylamine (1 : 1, v/v, 60 ml) was added and stirred at 80°C oil bath for 24 h. The reaction mixture was evaporated *in vacuo*. The residue was dissolved in a small volume of EtOAc and chromatographed on a silicagel column with EtOAc-*n*-Hexane (1 : 1) to give 8 (2.28 g, 76 %) as a white solid. :^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.8 (1H, s, 8-H), 7.34-7.26 (5H, m, -O-CH_2-$C_6\underline{H}_5$), 7.24-7.25 (5H, m, -NH-

CH_2-C_6H_5), 5.95 (1H, d, 1'-H), 5.3 (2H, d, -O-CH_2-C_6H_5), 4.74 (1H, t, 2'-H), 4.43-4.35 (2H, m, -NH-CH_2- C_6H_5), 4.18 (1H, s, 4'-H), 3.69-3.85 (2H, dd, 5'-H), 0.83-0.82 (9 H, s, *tert*-Butyl).

2-*O*-Benzyl-6-benzylamino-9-[5'-(*tert*-butyldimethylsilyl)-2',3'-bis-*O*-(methylthio)-thiocarbonyl-β-D-ribofuranosyl] purine (9) [$C_{34}H_{43}N_5O_5S_4Si$: Fw= 757.38]

Compoud **8** (0.9 g, 1.56 mmol) was reacted with CS_2 (0.45 ml, 4.6 mmol) in DMF (10 ml) in the presence of 5N aqueous NaOH solution (1 ml) at room temperature for 30 min. To this solution, MeI (0.25 ml, 4.5 mmol) was added dropwise. The stirring was continued for 1 h. The solvent was removed *in vacuo* and the residue was extracted with $CHCl_3$. The organic layer was washed with water, dried ($MgSO_4$) and concentrated. Purification of the oily residue by chromatography on a silicagel column using $CHCl_3$-MeOH (100 : 1) gave **9** (0.86 g, 73 %).: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.0 (1H, s, 8-H), 7.35-7.5 (5 H, m, -O-CH_2-C_6H_5), 7.28-7.35 (5H, m, -NH-CH_2-C_6H_5), 6.57 (1H, d, 1'-H), 6.55-6.53 (1H, t, 2'-H), 6.43-6.41 (1H, d, 3'-H), 6.1 (1H, d, -NH-CH_2-C_6H_5), 5.46 (2H, s, -O-CH_2-C_6H_5), 4.83 (2H, s, -NH-CH_2-C_6H_5), 4.5 (1H, s, 4'-H), 4.0-3.9 (2H, dd, 5'-H), 2.6 (3 H, s, S-CH_3), 2.54 (3H, s, S-CH_3), 0.97 (9H, s, *tert*-Butyl).

2-*O*-Benzyl-6-benzylamino-9-[5'-(*tert*-butyldimethylsilyl)-2',3'-*O*-thiocarbonyl-β-D-ribofuranosyl]purine (9')[$C_{31}H_{37}N_5O_5SSi$: Fw=619.2]

To a solution of compound **8** (0.9 g, 1.56 mmol) in dry DMF (8 ml) was added 1,1-thiocarbonyldiimmidazole (0.7 g, 3.92 mmol). After sirring at 80°C oil bath for 2 h, the reaction mixture was evaporated. The residue was chromatographed on a silicagel column using EtOAc-*n*-Hexane (1:1) to give **9'** (0.47 g, 48.7 %). : ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.7 (1H, s, 8-H), 7.6-7.4 (5H, m, O-CH_2-C_6H_5), 7.4-7.2 (5H, m, -NH-CH_2-C_6H_5), 6.6 (1 H, s, NH-$CH_2C_6H_5$), 6.3 (1H, d, 1'-H), 6.1 (1H, t, 2'-H), 5.4 (2 H, s, -O-CH_2-C_6H_5), 4.8 (2H, d, -NH-CH_2-C_6H_5), 4.4 (1H, s, 4'-H), 3.7 (2H, dd, 5'-H), 0.9 (9 H, s, *tert*-Butyl).

2-*O*-Benzyl-6-benzylamino-9-[5'-(*tert*-butyldimethylsilyl)-2',3'-didehydro-2',3'-dideoxy-β-D-ribofuranosyl] purine (10) [$C_{30}H_{37}N_5O_3$: Fw=543.09]

Method A. from (9) : A mixture of compound **9** (0.86 g, 1.14 mmol) and dry toluene (9 ml) was refluxed at 80°C oil bath under nitrogen. To this solution, α,α'-azobisisobutyronitrile (AIBN) (0.07 g, 0.43 mmol) and tributyltin hydride (1.22 ml, 4.56 mmol) in 9 ml dry toluene was added dropwise. After refluxing for 2 h, evaporation and silica gel chromatography using $CHCl_3$-MeOH (80:1) gave compound **10** (0.42 g, 68 %).

Method B. from (9') : To a mixture of compound **9'** (0.47 g, 0.76 mmol) and acetonitrile (4.5 ml), 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine (0.19 ml, 1.01 mmol) was added and stirred at room temperature for 8 h. The reaction mixture was evaporated and chromatographed on a silicagel column with $CHCl_3$-MeOH (80:1) to give **10** (0.09 g, 20 %). : ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 7.9 (1H, s, 8-H), 7.5-7.3 (5H, m, -O-CH_2-C_6H_5), 7.3-7.1 (5H, m, -NH-CH_2-C_6H_5), 7.0 (1H, d, 1'-H), 6.4 (1 H, t, 2'-H), 6.2 (1H, s, -NH-CH_2-C_6H_5), 6.0 (1H, t, 3'-H), 5.4 (2 H, d, -O-CH_2-C_6H_5), 5.0 (1H, m, 4'-H), 4.8 (2H, d, -NH-CH_2-C_6H_5), 4.1 (2H, m, 5'-H), 0.9 (9 H, s, *tert*-Butyl).

2-O-Benzyl-6-benzylamino-9-(2',3'-didehydro-2',3'-dideoxy-β-D-ribofuranosyl)purine(11)[$C_{24}H_{23}N_5O_3$:Fw=429.05]

To a solution of compound **10** (1.7 g, 3.13 mmol) in dry THF (15 ml) at 0°C was added a solution of Bu_4NF in THF (1.0 M, 0.23 ml). The mixture was stirred at 0°C for 1h. After evaporation, chromatography on a silicagel column using $CHCl_3$-MeOH (80 : 1) gave compound **11** (1.04 g, 77%). : ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 7.7 (1 H, s, 8-H), 7.5-7.3 (5H, m, -O-CH_2-C_6H_5), 7.3-7.1 (5 H, m, -NH-CH_2-C_6H_5), 7.0 (1H, d, 1'-H), 6.5 (1H, s, -NH-CH_2-C_6H_5), 6.3 (1H, t, 2'-H), 6.0 (1H, t, 3'-H), 5.4-5.2 (2H, m, -O-CH_2-C_6H_5), 4.8-5.1 (2H, d, -NH-CH_2-C_6H_5), 4.5 (1H, m, 4'-H), 3.8-4.0 (2H, m, 5'-H).

2',3'-dideoxyisoguanosine(12)[$C_{10}H_{13}N_5O_3$: Fw=251.05]

Compound **11** (0.3 g, 0.69 mmol) in CH_3OH (45 ml) was hydrogenated at 45 psi, 50°C in the presence of excess 10% Pd/C (0.5 g) for 24 h. The catalyst was filtered off through celite, and the filtrate was concentrated. The residue was purified by chromatography on a silicagel column using $CHCl_3$-MeOH (4:1) to obtain 0.12 g (70 %) of compound **12** : mp > 270°C (darken); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 7.9 (1H, s, 8-H), 6.76 (2H, s, NH_2), 5.98 (1H, dd, 1'-H), 4.2 (1H, m, 4'-H), 3.44 (2H, m, 5'-H), 1.97 (1H, t, 2'-H), 1.93 (1 H, t, 3'-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 25.57, 31.64, 62.91, 81.38, 83.96, 137.3, 156.3; HRFABMS calcd. m/z 252.1098 for $C_{10}H_{14}N_5O_3$, $(M+H)^+$, found 252.1096.

RESULTS AND DISCUSSION

We designed the scheme for synthesizing dideoxyisoguanosine effectively using protecting groups (Chu *et al.*, 1989). As iso-guanosine (Nair *et al.*, 1985) has 6-amino and 2-oxo groups in its purine base, it has high polarity and poor solubility which usually make purification laborious relative to other regular nucleo-sides. To overcome these troublesomes, we introduced protecting groups to intermediates. We obtained 6-[(4-methylphenyl)thio]-2-oxo-9-(2',3',5'-tri-*O*-acetyl-β-D-ribofuranosyl)

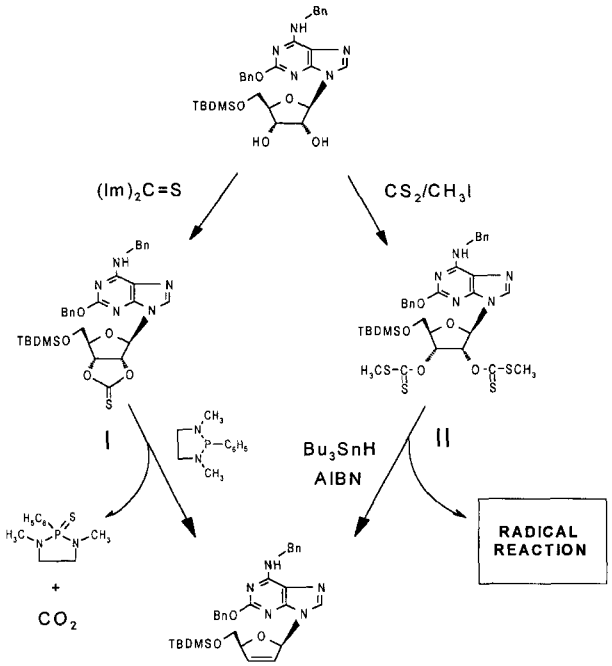


Fig. 1. The introduction of the double bond

-2,3-dihydropurine (**4**) *via* acetylation, chlorination, toluenthiol substitution and diazotization from guanosine using K. J. Divakar's method in a 63% yield. Compound **4** was treated with K_2CO_3, tetraethylammonium iodide and benzyl bromide in DMSO to protect 2-oxo group in base. Benzyl protected compound **5** was obtained in a high yield. Compound **5** was allowed to react sodium methoxide in methanol at room tempe-rature to give deacetylated form **6** of compound **5** at 2',3' and 5'-hydroxyl group in ribose sugar moiety. For introducing olefin at 2', 3'-diol, 5'-OH group in com-pound **6** was protected with *tert*-butyldimethylsilyl chloride and imidazole in DMF (Aizpurua *et al.*, 1985). A toluenethiol group in compound **7** was substituted with benzylamine in ethanol at 80°C oil bath for 24 h. This tri-protected intermediate make overcome poor solubility most purine nucleoside has and puri-fication easy in each step. Also, these protecting groups were easily removed from Pd/C reaction for reduction of olefin, which make needless additional reaction steps. We made comparison Corey-Winter reaction (Fig. 1. I) (Corey *et al.*, 1972) and Barton-deoxygenation reaction (Fig. 1. II) (Barton *et al.*, 1991) for introducing olefin to 2', 3' position in ribose sugar moiety. Barton deoxygenation method (yield 50%) which introduce double bond with tri-*n*-butyltin-hydride by radical reaction *via* bisxanthate using carbondisulfide and MeI was proved more effective in case of this scheme to synthesize 2',3'-dideoxyisoguanosine than Corey-Winter reaction (yield 10%) which use 1,3-dimethyl-2-phenyl-1,3-diazapho-spholidine *via* cyclic thionocarbonate for introducing olefin from vicinal diol.

Compound **10** was reacted with Bu_4NF in THF to furnish the deprotected compound **11**. Compound **11** in methanol was hydrogenated at 45 psi, 50°C with excess 10% Pd/C for 24 h to give final product **12**. During the reduction of olefin in ribose, debenzylation of benzyl ether at 2-position and benzyl amine at 6-position in base was accompanied. As the Pd/C reaction was little processed below 45 psi, the reaction condition, 45 psi and 24 h, should be observed strictly in last step. The dideoxy isoguanosine **12** was synthesized from guanosine in 10% overall yield. The biological activities including antitumor and antiviral activities for 2',3'-didexoy isoguanosine is now under studying.

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