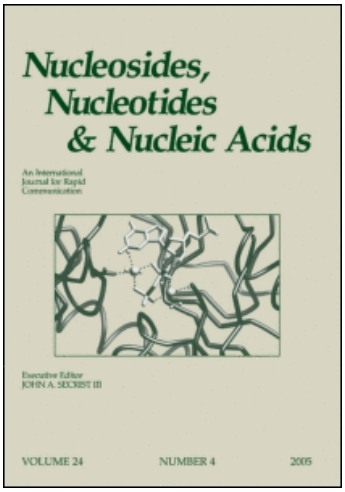

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Takayoshi Torii[a]; Kunisuke Izawa[a]; Dae Hyan Cho[b]; Doo Ok Jang[b]
[a] AminoScience Laboratories, Ajinomoto Co., Inc., Kawasaki, Japan [b] Department of Chemistry, Yonsei University, Wonju, South Korea

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SYNTHESIS OF 2′,3′-DIDEOXYINOSINE VIA RADICAL DEOXYGENATION

Takayoshi Torii and Kunisuke Izawa □ *AminoScience Laboratories, Ajinomoto Co., Inc., Kawasaki, Japan*

Dae Hyan Cho and Doo Ok Jang □ *Department of Chemistry, Yonsei University, Wonju, South Korea*

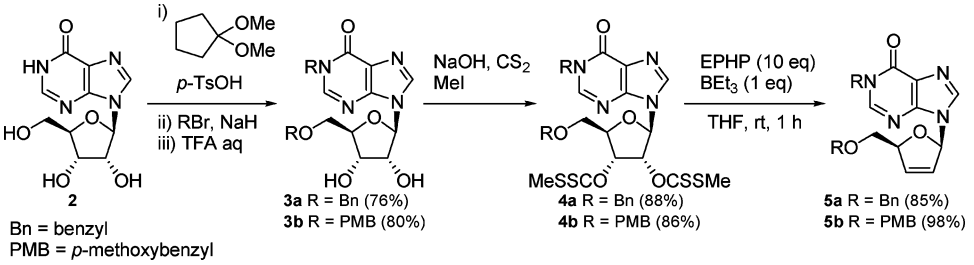
□ *A synthetic method for 2′,3′-dideoxyinosine (ddI) from inosine was established via radical deoxygenation of* N*1,5′-*O*-diprotected-2′,3′-bis-*S*-methyl dithiocarbonate of inosine derivatives. The radical deoxygenation proceeded smoothly to give the desired dideoxy compounds in good yields using 1-ethylpiperidinium hypophosphite and triethylborane. Benzyl or* p*-methoxybenzyl protection of inosine at the* N*1, 5′-*O*-positions were effective for the ddI synthesis.*

Keywords 2′,3′-Dideoxyinosine; radical deoxygenation; 1-ethylpiperidinium hypophosphite; *N*1 and 5′-*O*-protection; debenzylation

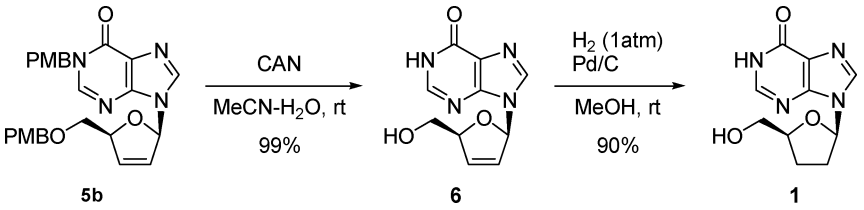
INTRODUCTION

2′,3′-Dideoxyinosine (ddI, **1**) was developed as a nucleoside reverse transcriptase inhibitor against human immunodeficiency virus for the treatment of acquired immune deficiency syndrome and was launched in 1991. We already have reported several synthetic methods of **1**.[1] Previously, Chu et al. reported that **1** is readily obtained by Barton deoxygenation via 2′,3′-bis-*S*-methyl dithiocarbonate.[2] This is one of the most straightforward methods to synthesize **1** from **2**, requiring only five steps. This method, however, requires an excess amount of tributyltin hydride for deoxygenation, and therefore purification of the desired product without using silica-gel chromatography is very difficult. In addition, the toxicity of tributyltin hydride is not acceptable for large-scale synthesis. Expensive TBDMS-Cl is also necessary for selective protection of the 5′-hydroxyl group of inosine. We previously reported the use of hypophosphorous acid and 1-ethylpiperidinium hypophosphite (EPHP) as radical reducing agents instead of tributyltin hydride for the deoxygenation of nucleosides.[3] We

Address correspondence to Kunisuke Izawa, AminoScience Laboratories, Ajinomoto Co., Inc., 1-1, Suzuki-cho, Kawasaki-ku, Kawasaki, 210-8681, Japan. E-mail: kunisuke_izawa@ajinomoto.com



SCHEME 1 Radical deoxygenation of **4**.



SCHEME 2 Deprotection of **5b**.

report here an application of this methodology to the synthesis of ddI (**1**). We also report efficient processes using more versatile benzyl and *p*-methoxybenzyl protection for the N1,5′-*O*-groups.

RESULTS AND DISCUSSION

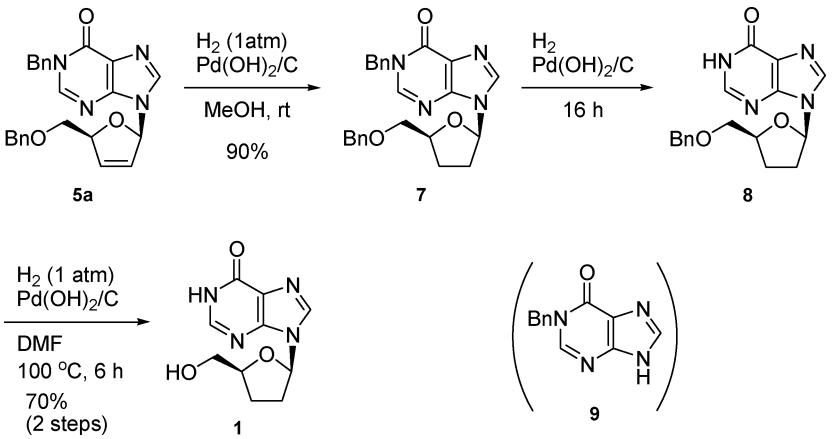
*N*1-Benzyl-5′-*O*-benzylinosine (**3a**) was synthesized from **2** through cyclopentylidene protection, followed by benzylation and deprotection of ketal.[4] *N*1-*p*-Methoxybenzyl-5′-*O*-(*p*-methoxybenzyl)inosine (**3b**) was prepared by the same method as **3a**, using *p*-methoxybenzyl bromide. Compounds **3a** and **3b** were converted into bis *S*-methyl dithiocarbonate derivatives **4a** and **4b** in high yields. Because the *N*1 position of **3a** and **3b** was protected by benzyl and *p*-methoxybenzyl, no *N*1-methylated byproduct was formed during the *S*-methylation.[2] Compounds **4a** and **4b** were transformed into 2′,3′-didehydro-2′,3′-dideoxy derivatives **5a** and **5b** by radical reduction using EPHP as a reducing agent and triethylborane as a radical initiator. The yield of **5a** and **5b** was 85% and 98%, respectively. In contrast to the case of tin reduction, the isolation and purification of **5** was easy because the yields were very high and there was no metal contamination (Scheme 1).

Cleavage of the *p*-methoxybenzyl groups of **5b** with ceric ammonium nitrate provided 2′,3′-didehydro-2′,3′-dideoxyinosine (d4I, **6**) in 99% yield, which was eventually transformed into ddI (**1**) by hydrogenation in 90% yield (Scheme 2).

On the other hand, cleavage of the benzyl groups of **5a** under conventional hydrogenolysis conditions with $Pd(OH)_2/C$ did not proceed, and the

TABLE 1 Debenzylation of **7**

Entry	Solvent	Temp.(°C)	H_2(atm)	Additive(eq)	Results
1	MeOH	rt	1	—	No reaction
2	MeOH	50	1	—	No reaction
3	MeOH	50	50	—	Complex mixture
4	DMF	80	1	—	9, major product
5	DMF	80	1	NaOH (2.5)	8, quant



SCHEME 3 Deprotection of **5a**.

reaction gave only the protected ddI derivative **7** in 90% yield. It has been reported that the benzyl group at the *N*1 of hypoxanthine and guanine,[5] and the *N*3 of uracil and thymine[4,6] is difficult to deprotect under hydrogenolysis conditions: a large amount of Pd catalyst[5a] or high temperature over 100°C[5b] is required. Therefore, we examined cleavage of the benzyl groups of **7** under hydrogenolysis conditions using $Pd(OH)_2/C$, whose ratio to **7** was 0.2 by weight (Table 1). Compound **7** remained intact when the reaction temperature was raised to 50°C (entry 2). Under high H_2 pressure, compound **7** decomposed to give a complex mixture (entry 3). Unexpectedly, a benzyl group was deprotected to give **8** with $Pd(OH)_2/C$ at 80°C in DMF by adding aq. NaOH under 1 atm of H_2 (entry 5). In the absence of NaOH, cleavage of a glycosyl bond of **7** occurred, providing **9** as a major product (entry 4). The structure of 5′-*O*-benzyl-2′,3′-dideoxyinosine (**8**) was identified by NMR-study.[7] Compound **8** was eventually transformed into ddI (**1**) simply by elevating the hydrogenolysis conditions to 100°C for 6 h under 1 atm of H_2. The isolated yield of **1** from **7** was 70% (Scheme 3).

In conclusion, we established a synthetic method for ddI (**1**) from inosine (**2**) in 36% overall yield via benzyl-protected compound **3a**, and in 60% overall yield via *p*-methoxybenzyl protected compound **3b**. We also report that both EPHP/BEt_3 reduction and inexpensive benzyl or

p-methoxybenzyl protection at the *N*1, 5′-*O*-position of inosine (**2**) were effective for the synthesis of ddI (**1**).

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7. ^{1}H-NMR (400 MHz, DMSO-d$_6$) of **7**: δ 2.07–2.12 (2H, m, H-2′ or H-3′), 2.42–2.47 (2H, m, H-2′ or H-3′), 3.55 (1H, dd, $J = 10.6$, 5.4 Hz, H-5′$_a$), 3.65 (1H, dd, $J = 10.6$, 3.6 Hz, H-5′$_b$), 4.23–4.29 (1H, m, H-4′), 4.49 (2H, s, OCH$_2$Ph), 5.23 (2H, s, NCH$_2$Ph), 6.23 (1H, dd, $J = 6.8$, 3.3 Hz, H-1′), 7.24–7.34 (10H, m, aromatic), 8.25 (1H, s, H-8), 8.59 (1H, s, H-2). ^{1}H-NMR (400 MHz, DMSO-d$_6$) of **8**: δ 2.05–2.12 (2H, m, H-2′ or H-3′), 2.36–2.48 (2H, m, H-2′ or H-3′), 3.56 (1H, dd, $J = 10.5$, 5.5 Hz, H-5′$_a$), 3.65 (1H, dd, $J = 10.5$, 3.8 Hz, H-5′$_b$), 4.21–4.26 (1H, m, H-4′), 4.50 (2H, s, OCH$_2$Ph), 6.19 (1H, dd, $J = 6.7$, 3.8 Hz, H-1′), 7.24–7.36 (5H, m, aromatic), 8.00 (1H, s, H-8), 8.12 (1H, s, H-2).