JOC Article

Solvent Effect Observed in Nucleophilic Substitution of 4′-(Benzoyloxy)cordycepin with $AlMe_3$: Stereochemical Evidence for S_Ni Mechanism

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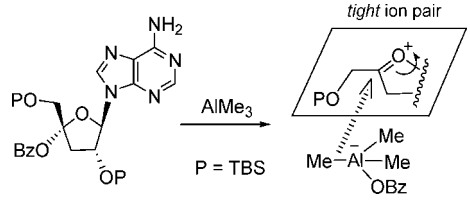

Nucleophilic substitution between the 4′-benzoyloxy derivative of cordycepin (3′-deoxyadenosine) and $AlMe_3$ proceeds mostly with retention of configuration at the 4′-position: the 4′-benzoyloxy substrate having the β-D-configuration (**8a**) gave the 4′-methylated β-D-nucleoside (**9a**) with a high diastereomeric excess, while the substrate **8b** having the opposite 4′-configuration gave the corresponding α-L-isomer (**9b**) with a comparatively lower stereoselectivity. The S_Ni mechanism is proposed for this reaction (from **8** to **9**). The polarity of the solvent has a significant influence on the stereoselectivity, especially for the formation of **9b**.

Introduction

Nucleosides having a leaving group either at the 1′- or 4′-position, upon reacting with AlR_3, provide an intermediate stabilized as an oxacarbenium ion, which is exemplified in Schemes 1 and 2 in our previous reports. In the reaction depicted in Scheme 1,[1] coordination of $AlMe_3$ to the carbonyl oxygen atom of the 1′-pivaloyloxy group of **1** is followed by the formation of the oxacarbenium intermediate **2**. Nucleophilic transfer of the activated methyl ligand of the aluminate takes place exclusively from the α-face to give **3**, presumably due to either neighboring group participation or steric shielding by the 2′-bromine atom.

In the case of Scheme 2,[2] where the intermediate **5** is generated from **4**, there are two competing modes of nucleophilic attack at the 4′-position: one is an intramolecular attack of the oxygen atom of the 5′-*O*-benzoyl group leading to **6**, and the other is an intermolecular ligand transfer from the aluminate forming **7**. Both products (**6** and **7**) have the 4′-configuration arising from steric shielding by the proximal 3′-silyloxy substituent.

Preparation of the cordycepin (3′-deoxyadenosine) derivative having a benzoyloxy leaving group at the 4′-position (**8**) has recently been reported from our laboratory.[3] To investigate the stereochemical aspects of nucleophilic substitution with $AlMe_3$, we considered that **8** would be a suitable substrate, because its 3′-deoxy structure excludes both the possibility of proximal steric hindrance as well as neighboring group participation. The present study was motivated by the above consideration.

Results and Discussion

The reaction between $AlMe_3$ and **8** was examined first by using a mixture of the two diastereomers. A solution of **8** (**8a**/**8b** = 1/2)[4] in CH_2Cl_2 was treated at 0 °C with dropwise addition of $AlMe_3$ (5 equiv, 1.05 M hexane solution), and the resulting mixture was then kept stirring at room temperature for 2.5 h. After aqueous workup with saturated NH_4Cl, the reaction mixture was filtered through a Celite pad. Three products **9a**, **9b**, and **10** (Scheme 3) were collected following silica gel column chromatography, and the ratio of the products was

(1) Itoh, Y.; Haraguchi, K.; Tanaka, H.; Gen, E.; Miyasaka, T. *J. Org. Chem.* **1995**, *60*, 656–662.
(2) Haraguchi, K.; Sumino, M.; Tanaka, H. *J. Org. Chem.* **2006**, *71*, 4433–4438.
(3) Kubota, Y.; Kunikata, M.; Ishizaki, N.; Haraguchi, K.; Odanaka, Y.; Tanaka, H. *Tetrahedron* **2008**, *64*, 2391–2396.
(4) For NOE data of **8a** and **8b**, see ref 3.
(5) The values of dipole moment and dielectric constant in Table 1 were taken from: *Lange's Handbook of Chemistry*, 15th ed.; Dean, J. H., Ed.; McGraw-Hill: New York, 1999.

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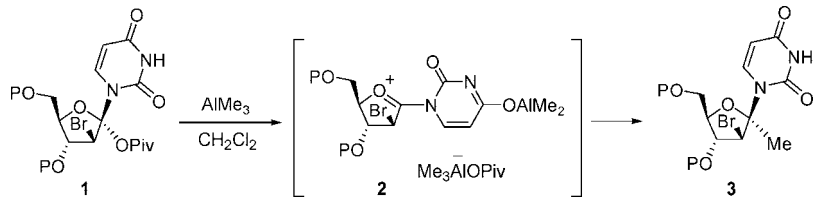
SCHEME 1



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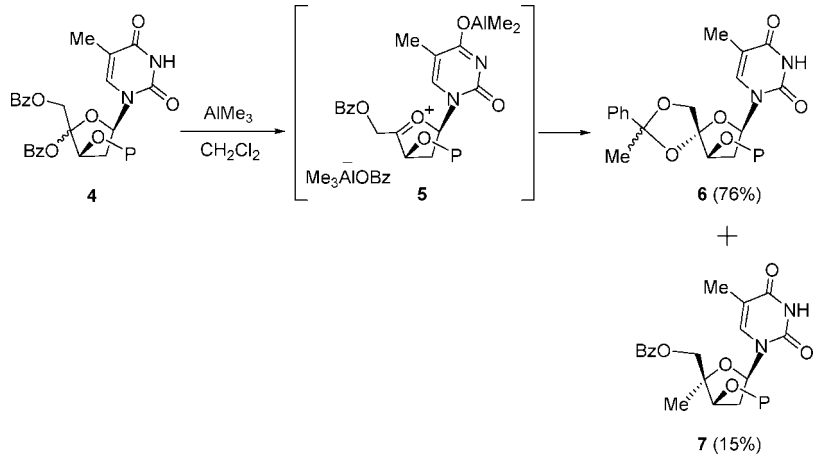


SCHEME 3

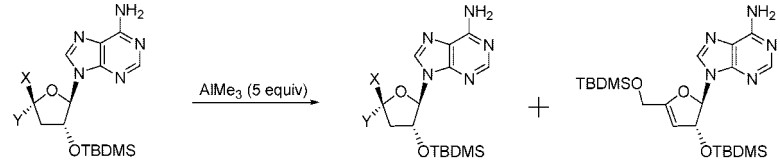


TABLE 1. Reaction between 8 and $AlMe_3$[a]

entry	substrate	solvent	dipole moment (D)	dielectric constant (ε)	time (h)	conversion (%)	ratio of products[b] **9a**:**9b**:**10**	de[c] (%)
1	**8** (**8a**/**8b** = 1/2)	CH_2Cl_2	1.6	9.0	2.5	100	41:41:18	0
2	**8a**	CH_2Cl_2	1.6	9.0	1	100	82:3:15	93
3	**8b**	CH_2Cl_2	1.6	9.0	6	100	21:70:9	54
4	**8a**	CCl_4	0	2.2	6	99	97:1:2	98
5	**8b**	CCl_4	0	2.2	6	99	10:87:3	79
6	**8a**	cyclohexane	0	2.0	6	97	93:4:3	92
7	**8b**	cyclohexane	0	2.0	6	99	8:86:6	85
8	**8a**	$MeCCl_2Me$	2.62	11.4	3	90	54:3:43	89
9	**8b**	$MeCCl_2Me$	2.62	11.4	7	95	16:45:39	48

[a] All reactions were carried out with 5 equiv of $AlMe_3$ under positive pressure of dry Ar. After dropwise adddition of $AlMe_3$ to a solution of 8 at 0 °C, the reaction mixture was stirred at room temperature. [b] Determined by ^{1}H NMR spectroscopy by integrating H-1′ of the respective product. [c] Diastereomeric excess.

analyzed by ^{1}H NMR spectroscopy. As shown in entry 1 of Table 1,[5] the 4′-methylated products of β-D- (**9a**)[6] and α-L- (**9b**)[6] isomers were formed in equal amounts. A small amount of the elimination product **10**[7] was also formed.

Additionally, when the reaction in Scheme 3 was carried out in THF, no reaction took place. This fact contrasts with our previous observation that an epoxy-sugar nucleoside undergoes ring-opening with $AlMe_3$ even in ethereal solvents such as THF[7] and suggests that $AlMe_3$ is unable to coordinate with the 4′-benzoyloxy group in the presence of THF.

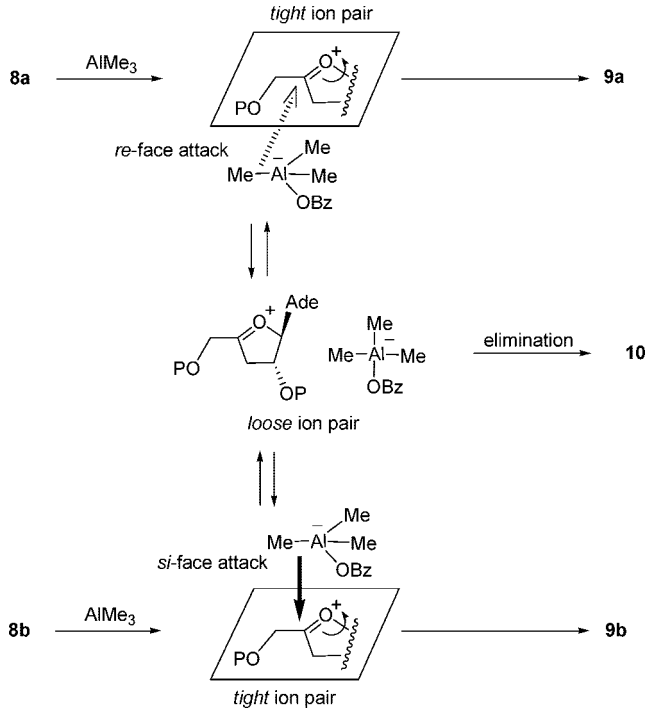
Since the involvement of an oxacarbenium intermediate was anticipated, we initially thought that the separate use of **8a** and **8b** in this reaction would lead to the same result as that of entry 1. However, both **8a** and **8b** gave preferentially the product resulting from retention of configuration at the 4′-position

(6) The NOEs of **9a** and **9b** were measured in $CDCl_3$. For **9a**: H-5′b/H-8 (0.9%), 4′-Me/H-1′ (3.7%); for **9b**: H-8/4′-Me (1.2%), H-1′/H-5′b (0.6%). Of the two protons at the 5′-position, the one that appears at a higher field is designated as H-5′a and the other as H-5′b.

(7) Kubota, Y.; Haraguchi, K.; Kunikata, M.; Hayashi, M.; Ohkawa, M.; Tanaka, H. *J. Org. Chem.* **2006**, *71*, 1099–1103.

(8) The reactions corresponding to entries 2 and 3 were also carried out by using 3′,5′-bis-*O*-triethylsilyl- and 3′,5′-bis-*O*-(*tert*-butyldiphenylsilyl)-protected substrates. However, no significant difference was seen in terms of diastereoselectivity.

SCHEME 4



(entries 2 and 3).[8] When a comparison was made in terms of diastereomeric excess (de), the reaction of **8a** (entry 2) gave a much higher selectivity than that of **8b** (entry 3). These findings led us to assume the reaction mechanism depicted in Scheme 4.

Namely, if the aluminate ($[Me_3AlOBz]^-$) formed after coordination to the 4′-benzoyloxy group of the respective substrate remained on the side it departed, forming a *tight* ion pair, nucleophilic attack of its methyl ligand inevitably takes place from the same side resulting in retention of configuration, an S_Ni (*substitution nucleophilic internal*) mechanism. An additional assumption that can be made from entry 3 is that such spatial disposition of the aluminate would become less favored at the β-face of the furanose ring due to the presence of the bulky base moiety, causing an equilibrium shift from a *tight* ion pair to a *loose* ion pair, which is consistent with a significantly lower de observed in the reaction of **8b**.

The above arguments are, of course, meaningful only on the assumption that epimerization at the 4′-position of **8a** and **8b** is not involved during their reaction with $AlMe_3$. When the reaction of **8b** in entry 3 was quenched after 15 min and the recovered substrate (recovery: 27%) was analyzed by HPLC as well as ^{1}H NMR spectroscopy, no contamination of the 4′-epimer (**8a**) was observed.[9] It is worth mentioning that, at this stage, the 4′-methylated product **9a** resulting from inversion of configuration was already present in the reaction mixture. These facts suggest that, once the aluminate is formed, transfer of its benzoyloxy ligand to the oxacarbenium ion does not take place.

One would assume that an equilibrium between the tight and loose ion pairs shown in Scheme 4 would be influenced by the polarity of the reaction solvent: in a less polar solvent, the tight ion pair becomes more favored (and vice versa). This assumption led us to the expectation that the observed lower de for **9b** in entry 3 could be improved by carrying out the reaction in nonpolar solvents. This was examined by employing CCl_4 or cyclohexane. Entries 4−7 clearly show that, while no dramatic change was observed in the de of **9a** (already high at 93 in entry 2), the expected improvement in de was certainly found for **9b**.

The reverse was true. In the polar solvent, 2,2-dichloropropane (entries 8 and 9), a lower de resulted, especially in the formation of **9b**. An additional feature observed in the reactions carried out in 2,2-dichloropropane is the fact that elimination pathway leading to **10** became a significant event. It is not clear if the formation of **10** from **8a** and **8b** entirely comes from the loose ion pair, but it is certainly true that the polarity of the solvent has a significant effect to the formation **10**.

To conclude, we have observed that nucleophilic substitution of the 4′-(benzoyloxy)cordycepin (**8**) with $AlMe_3$ proceeds mostly with retention of configuration at the 4′-position by carrying out the reaction of **8a** (β-D-isomer) and **8b** (α-L-isomer) separately. The S_Ni mechanism has been proposed for this reaction. The polarity of the reaction solvent has significant influence, especially for the reaction of **8b**: in nonpolar solvents, the de of **9b** was considerably improved. An additional observation in the reaction of **8a** and **8b** in a polar solvent is that the elimination pathway leading to **10** became significant, which we attribute to the formation of loose ion pairs.

Finally, we would like to mention a related study. The reaction of $AlEt_3$ with optically active α-phenethyl chloride, employing EtCl (2.05 D, ε 9.45)[5] as the reaction solvent at −65 °C, resulted in predominant racemization with only 4% net retention.[10] Although nucleophilic substitution of alkyl chlorides[10−12] or allyl, benzyl, and cyclopropylmethyl esters[13,14] using trialkylaluminums has been reported, there has been no study carried out to clarify solvent effects on the stereochemical outcome of this type of reaction.

Experimental Section

4′-Methyl-2′,5′-bis-*O*-(*tert*-butyldimethylsilyl)cordycepin (9a) and 9-[2,5-bis-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-4-methyl-α-L-arabinofuranosyl]adenine (9b) from a Mixture of 8a and 8b (Entry 1 in Table 1). A solution of **8** (**8a**/**8b** = 1/2, 50 mg, 0.083 mmol) in CH_2Cl_2 (3.0 mL) was cooled to 0 °C under a positive pressure of dry Ar. To this was added $AlMe_3$ (1.03 M hexane solution, 0.40 mL, 0.413 mmol), and the reaction mixture was allowed to stir at rt for 2.5 h. After being quenched by addition of saturated aqueous NH_4Cl, the reaction mixture was filtered through a Celite pad. The filtrate was extracted with CH_2Cl_2. Column chromatography (hexane/EtOAc = 1/2) of the organic extract gave **9** (38 mg, 76%, **9a**/**9b** = 1/1) as a foam. HPLC separation ($CHCl_3$/MeOH = 90/1) gave analytically pure **9a** (t_R = 18.3 min, foam) and **9b** (t_R = 21.7 min, foam).

Physical data for 9a: UV (MeOH) λ_{max} 260 nm (ε 14200), λ_{min} 229 nm (ε 1600); ^{1}H NMR ($CDCl_3$) δ −0.11, −0.07, 0.12, and 0.13 (12H, each as s), 0.82 and 0.95 (18H, each as s), 1.39 (3H, s), 1.85 (1H, dd, J = 5.9 and 12.8 Hz), 2.51 (1H, dd, J = 6.8 and

(9) This "early quenching" experiment was also carried out for the reactions in entries 2, 4, 5, 8, and 9. As a result, it was confirmed that the substrate (**8a** or **8b**) recovered from these experiments did not contain the respective 4′-epimer as evidenced by ^{1}H NMR analysis.

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(14) Itoh, A.; Oshima, K.; Sasaki, S.; Yamamoto, H.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1979**, 4751–4754.

12.8 Hz), 3.49 (1H, d, J = 10.6 Hz), 3.75 (1H, d, J = 10.6 Hz), 4.78 (1H, ddd, J = 4.4, 5.9, and 6.8 Hz), 5.61 (2H, br), 6.05 (1H, d, J = 4.4 Hz), 8.24 (1H, s), 8.34 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.4, −5.3, −5.2, −5.1, 17.8, 18.5, 24.9, 25.6, 26.0, 40.8, 69.5, 77.6, 85.7, 90.5, 119.8, 139.2, 150.0, 152.9, 155.3; FAB-MS (*m*/*z*) 494 (M^+ + H). Anal. Calcd for $C_{23}H_{43}N_5O_3Si_2$: C, 55.94; H, 8.78; N, 14.18. Found: C, 55.72; H, 8.87; N, 14.12.

Physical data for 9b: UV (MeOH) λ_{max} 260 nm (ε 14800), λ_{min} 228 nm (ε 2700); ^{1}H NMR ($CDCl_3$) δ −0.07, −0.01, 0.08, and 0.09 (12H, each as s), 0.84 and 0.93 (18H, each as s), 1.44 (3H, s), 2.09 (1H, dd, J = 6.8 and 13.2 Hz), 2.25 (1H, dd, J = 4.9 and 13.2 Hz), 3.60 (1H, d, J = 9.8 Hz), 3.71 (1H, d, J = 9.8 Hz), 5.09 (1H, ddd, J = 3.7, 4.9, and 6.8 Hz), 5.67 (2H, br), 5.88 (1H, d, J = 3.7 Hz), 7.91 (1H, s), 8.35 (1H, s); ^{13}C NMR ($CDCl_3$) δ −5.4, −5.3, −5.1, −5.0, 17.8, 18.3, 24.7, 25.6, 25.9, 40.8, 69.3, 76.1, 86.1, 92.6, 120.5, 139.4, 149.6, 152.9, 155.4; FAB-MS (*m*/*z*) 494 (M^+ + H). Anal. Calcd for $C_{23}H_{43}N_5O_3Si_2$: C, 55.94; H, 8.78; N, 14.18. Found: C, 55.87; H, 8.90; N, 14.09.

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Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectra of **9a** and **9b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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