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Syntheses of the marine ascidian purine aplidiamine and its 9-β-D-ribofuranoside

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Abstract

The title nucleoside **9** was synthesized by alkylation of 8-oxoadenosine (**7**) with 4-benzyloxy-3,5-dibromobenzyl bromide, followed by Dimroth rearrangement and acid hydrolysis. 2'-Deoxy version of this reaction sequence accomplished the first synthesis of aplidiamine (**6**).

Keywords: benzylation; hydrolysis; marine metabolites; purines

Aplidiamine (**6**), which has been isolated from the marine ascidian *Aplidiopsis* sp. [1], is the newest member of a small family [2] of naturally occurring 8-oxoadenine derivatives. This paper reports the first synthesis of **6** following the reaction sequence (Scheme 1), which has been established in our laboratory [3,4] for the synthesis of *N*-methyl-8-oxo-adenine (**5a**) from 8-oxoadenosine (**7**) through **1a** and **3a**.

Thus **7** was treated with 4-benzyloxy-3,5-dibromobenzyl bromide, which was prepared from 3,5-dibromo-4-hydroxybenzaldehyde [5] by treatment with $PhCH_2Br$ in the presence of NaH, followed by sequential treatment with $NaBH_4$ and PBr_3, in $AcNMe_2$ at 50 °C for 111 h to afford the nucleoside **1b**. This was heated in boiling 1 N aqueous NaOH for 1 h to produce the rearranged nucleoside **3b** in 58% overall yield. Hydrolysis of **3a** takes place so slowly in aqueous HCl to yield **5a** [4] that **3b** would produce the target purine **6** through the nucleoside **9** under similar conditions. Indeed, $\mathbf{9}\cdot H_2O$ [mp 167.5—169 °C (dec.); ^{1}H NMR [$(CD_3)_2SO$] δ: 4.58 (2H, d) and 7.03 (1H, t) (J = 5.9 Hz each, CH_2NH), 7.54 (2H, s) and 9.88 (1H, br s) ($C_6H_2Br_2OH$), 8.13 [1H, s, C(2)-H], 10.31 [1H, br s, N(7)-H]. *Anal.* Calcd for $C_{17}H_{17}Br_2N_5O_6\cdot H_2O$: C, 36.13; H, 3.39; N, 12.39. Found: C, 36.31; H, 3.17; N, 12.28.] was obtained in 53% yield by heating **3b** in 1 N aqueous HCl for 1 h. More drastic conditions were necessary for removal of the sugar moiety of **9**. Treatment of **3b** in boiling 2 N aqueous HCl for 48 h [4] mainly gave 8-oxoadenine (type **5**: R = H).

We then prepared the 2'-deoxy analogue **4b**, whose glycosidic bond was expected to be much more susceptible to acid [6], from 2'-deoxy-8-oxoadenosine (**8**) [7] in 74% yield. On treatment with boiling 1 N aqueous HCl, **4b** was quickly converted into $\mathbf{5b}\cdot 1/2H_2O$ [mp 250—251 °C (dec.); ^{1}H NMR [$(CD_3)_2SO$] δ: 4.64 (2H, d) and 6.94 (1H, t) (J = 5.9 Hz each, CH_2NH), 4.96 (2H, s) and 7.36—7.59 (5H, m) ($PhCH_2$), 7.69 (2H, s, $C_6H_2Br_2$), 8.06 [1H, s,

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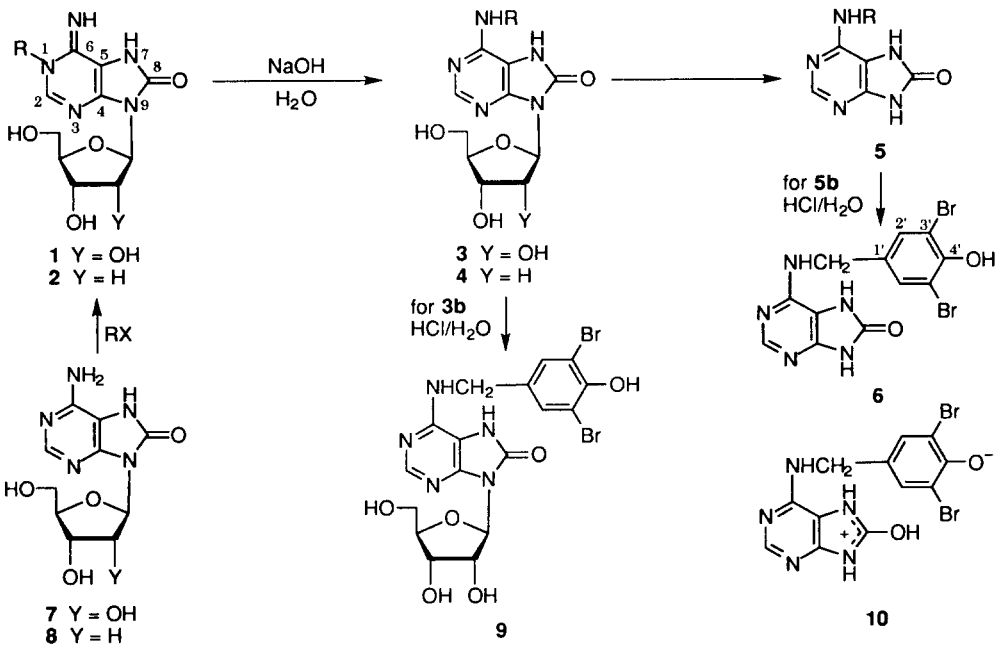
C(2)-H], 9.86 [1H, br s, N(7)-H], 11.37 [1H, br s, N(9)-H]. *Anal.* Calcd for $C_{19}H_{15}Br_2N_5O_2 \cdot 1/2H_2O$: C, 44.38; H, 3.14; N, 13.62. Found: C, 44.59; H, 3.06; N, 13.56.] and then **6**·H_2O [mp 239—239.5 °C (dec.). *Anal.* Calcd for $C_{12}H_9Br_2N_5O_2 \cdot H_2O$: C, 33.28; H, 2.56; N, 16.17. Found: C, 33.36; H, 2.55; N, 16.29.] was obtained in 78% yield after heating **5b** in 1 N aqueous HCl for 1 h. The ^1H and ^{13}C NMR spectra of this sample were identical with those [1] reported for aplidiamine,[1] confirming the correctness of the gross structure assigned to this marine metabolite.



Scheme 1

However, its close NMR spectral similarity to the benzyl ether **5b** indicates that the undissociated structure **6** is preferable to the zwitterion **10** [1]. HMBC experiments with the present sample show that the OH proton (δ 9.87) correlates with C3' (δ 111.9); the NH protons (δ 9.83 and 11.33) correlate with C4 (δ 147.4), C5 (δ 105.6), and C8 (δ 152.7), further supporting the correctness of the structure **6**.

[1] Kang H, Fenical W. Tetrahedron Lett. 1997;38:941–944.
[2] For other members, see Itaya T, Takada Y, Kanai T, Kaneko M, Fujii T. Chem. Pharm. Bull. 1997;44:1582–1588.
[3] Saito T, Kanai T, Fujii T. Chem. Pharm. Bull. 1993;41:1850–1852.
[4] Itaya T, Takada Y, Kanai T, Fujii, T. Chem. Pharm. Bull. 1996;44:2318–2321.
[5] Kassühlke KE, Faulkner DJ. Tetrahedron. 1991;47:1809–1814.
[6] Fujii T, Saito T, Iguchi K. Chem. Pharm. Bull. 1994;42:495–499 and references cited therein.
[7] Wood ML, Esteve A, Morningstar ML, Kuziemko GM, Essigmann JM. Nucleic Acids Res. 1992;20:6023–6032.

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