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First synthesis of 2′,3′-epimino-carbocyclic nucleosides

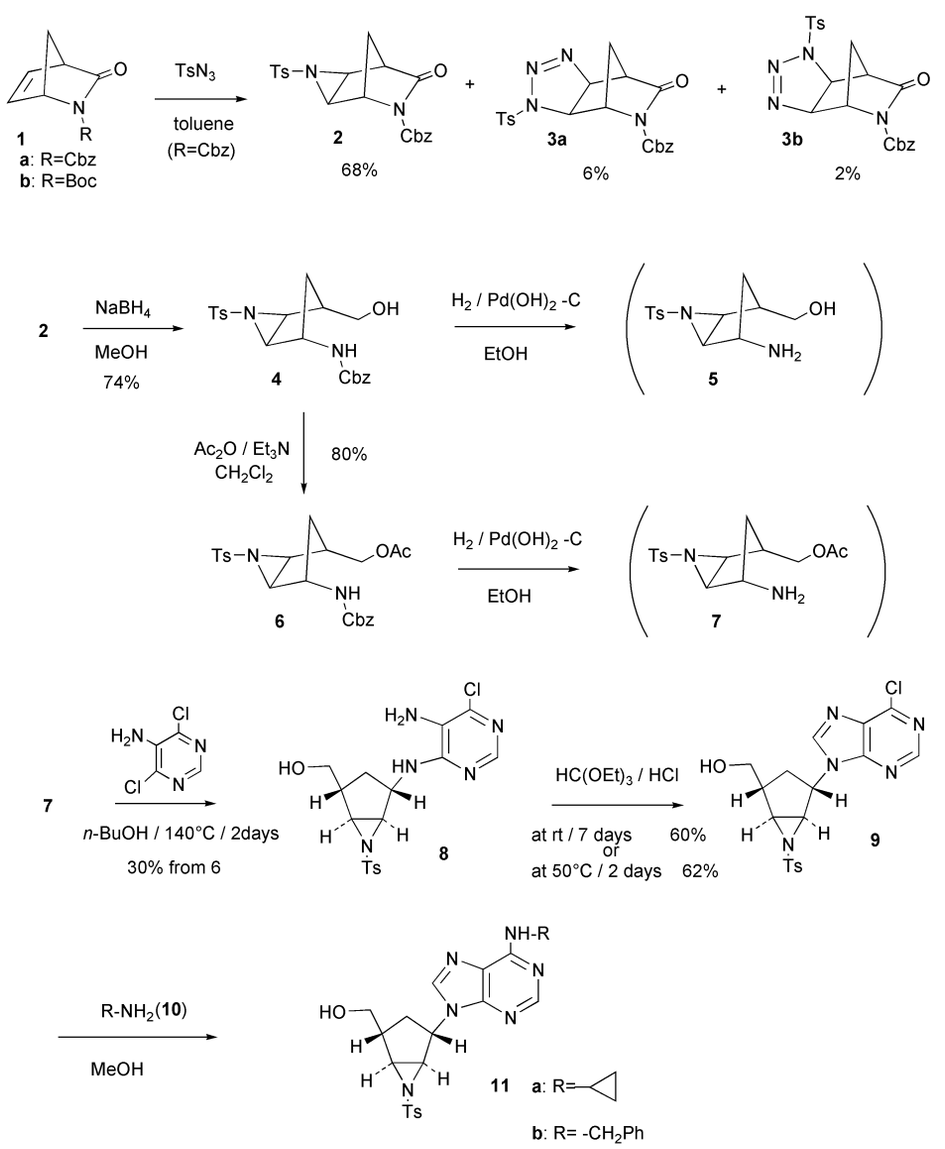
Minoru Ishikura,* Atsushi Murakami and Nobuya Katagiri
Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido, Ishikari-Tobetsu, Hokkaido 061-0293, Japan. E-mail: ishikura@hoku-iryo-u.ac.jp; Fax: (+81)-(0)1332-3-1245

Received 7th November 2002, Accepted 16th December 2002
First published as an Advance Article on the web 7th January 2003

The preparation of 2′,3′-epimino-carbocyclic analogues of adenosine is reported. The reaction of *p*-tosyl azide with *N*-substituted 2-azabicyclo[2.2.1]hept-5-en-3-one (ABH) (1a) provided aziridine-fused ABH (2), which was converted to 2′,3′-epimino-carbocyclic nucleosides (11).

Among recent efforts addressed at developing potent antiviral nucleosides,[1] understanding the role of conformationally constrained sugar rings built on a bicyclo[3.1.0]hexane template has been the subject of a wealth of systematic studies, wherein a number of methano- and epoxy-nucleoside derivatives have been reported.[2] Nevertheless, no attention has been denoted to 2′,3′-methano-carbocyclic nucleosides, prompting us to investigate the preparation and biological activities of 2′,3′-methano-carbocyclic nucleosides as a promising category of 2′,3′-dideoxynucleosides that have been employed as potent chemotherapeutic agents.[3] Thus, we have previously reported the first preparation of 2′,3′-methano-carbocyclic analogues of adenosine,[4] whose key reaction features included 1,3-dipolar or palladium-catalyzed [2+1] cycloaddition of diazomethane to *N*-substituted 2-azabicylo[2.2.1]hept-5-en-3-ones (ABH) (**1**), followed by the conversion to bicyclo[3.1.0]hexane template.

In due course, we have also become interested in the preparation and testing of the biological activities of 2′,3′-epimino-carbocyclic nucleosides. To our knowledge, no epimino-carbocyclic nucleosides have been prepared, and there are only a few antecedents to epimino-nucleosides in the literature.[5]



Scheme 1

DOI: 10.1039/b210963h

In our synthetic scheme, it was envisaged that 6-azabicyclo[3.1.0]hexane is a possible intermediate for the construction of 2′,3′-epimino-carbocyclic nucleosides. Thus, we have previously disclosed the formation of 6-azabicyclo-[3.1.0]hexane based on the use of high-pressure promoted 1,3-dipolar cycloaddition of azides [$(PhO)_2P(O)N_3$, EtO_2CN_3, PhN_3] to **1**, followed by photolysis of the resulting triazolines.[6] Alternatively, the reaction of TsN_3 with **1a** under thermal conditions was found to enable the concise formation of aziridine-fused ABH (**2**). Herein, we describe the first preparation of 2′,3′-epimino-carbocyclic nucleosides (**11**) *via* **7** which is readily available from **2** (Scheme 1).

Since acyl azides are known to be the most prominent acyl nitrene precursors, nitrene-addition to the double bond of **1a** was first attempted by heating with azides [$(PhO)_2P(O)N_3$, EtO_2CN_3] at 110 °C in toluene.[7] However, only a slight amount of aziridine-fused ABH was obtained. On the other hand, similarly heating TsN_3 with **1a** in toluene at 110 °C for 2 h readily produced aziridine-fused ABH (**2**) as crystals in 68% yield, along with the formation of triazolines (**3**) (**3a** in 6%, **3b** in 2%) as minor products. Although the previous photolysis of triazolines provided aziridine-fused ABHs in acceptable yields,[6] an attempted conversion of **3** to **2** by photolysis with a high-pressure mercuric lamp afforded a complex mixture. On the other hand, **3** was recovered unaltered even after heating in toluene at 110 °C for 1 h.

Next, the conversion of **2** to the aimed 2′,3′-epimino-carbocyclic nucleoside (**11**) was undertaken, during which the aziridine ring was successfully shown to be stable. Reductive cleavage of the amide bond (N–CO) of **2** with $NaBH_4$ in MeOH smoothly provided 6-azabicyclo[3.1.0]hexane (**4**) in 74% yield. Subjection of amine **5**, derived from **4** by removal of the *N*-Cbz group, to the reaction with 5-amino-4,6-dichloropyrimidine in *n*-BuOH at 140 °C gave complex mixtures, probably due to the undesirable nucleophilic attack of the unprotected hydroxy group on the aziridine ring. Alternatively, **4** was converted to acetate **6**, and the *N*-Cbz group in **6** was removed by catalytic hydrogenation, generating **7**. Without purification, **7** was submitted to a reaction with 5-amino-4,6-dichloropyrimidine in *n*-BuOH at 140 °C for 2 days, leading to pyrimidine **8** in 30% yield based on **6**. A longer reaction time (7 days) was required to enable the conversion of **8** to purine **9** in 60% yield by treatment with orthoethyl formate in the presence of HCl at room temperature. A reduction in time (2 days) was rendered by heating **8** with orthoethyl formate in the presence of HCl at 50 °C to give rise to **9** in 62% yield, in which the aziridine ring withstood even the increased reaction temperature. Then, heating **9** with amines **10** in MeOH at 50 °C provided 2′,3′-epimino-carbocyclic nucleosides (**11**).[8]

In summary, the first synthesis of 2′,3′-epimino-carbocyclic analogues of adenosine (**11**) was attained through the [2 + 1] cycloaddition reaction of nitrene generated from TsN_3 to ABH (**1a**). The resulting **2**, having an *N*-Ts-aziridine ring, was readily converted to 2′,3′-epimino-carbocyclic nucleosides (**11**) through a series of chemical transformations. Removal of the Ts group in **11** is under investigation, and will be reported in due course.

Acknowledgements

This work was supported in part by a Grant-in Aid for Scientific Research (No. 13672226) from the Ministry of Education, Culture, Sports, Science and Technology of Japan. The authors thank Kuraray Co., Ltd. for providing the ABH.

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8 **11a**: mp 174 °C (MeOH). ^{1}H-NMR (CD_3OD) δ: 0.47–0.51 (m, 2H), 0.69–0.75 (m, 2H), 1.68 (d, 1H, J = 13.7 Hz), 1.88 (dd, 1H, J = 7.4, 13.7 Hz), 2.39 (s, 1H), 2.44 (s, 3H), 2.58–2.63 (m, 1H), 2.90 (d, 1H, J = 9.7 Hz), 3.44 (td, 1H, J = 2.3, 9.7 Hz), 3.51 (s, 1H), 3.99 (d, 1H, J = 7.4 Hz), 4.19 (s, 1H), 7.39 (d, 2H, J = 8.0 Hz), 7.77 (d, 2H, J = 8.0 Hz), 7.93 (s, 1H), 8.12 (s, 1H). ^{13}C-NMR (CD_3OD) δ: 7.4, 7.5, 21.2, 25.0, 37.4, 41.4, 54.3, 60.1, 62.4, 73.1, 127.9, 130.8, 138.9, 144.9, 155.9, 157.9, 164.1. **11b**: mp 173 °C (MeOH). ^{1}H-NMR (CD_3OD) δ: 1.68 (d, 1H, J = 13.7 Hz), 1.90 (dd, 1H, J = 7.4, 13.7 Hz), 2.39 (s, 1H), 2.44 (s, 3H), 2.93 (d, 1H, J = 9.1 Hz), 3.48 (d, 1H, J = 9.1 Hz), 3.53 (s, 1H), 4.00 (d, 1H, J = 7.4 Hz), 4.19 (s, 1H), 4.53 (d, 1H, J = 15.4 Hz), 4.59 (d, 1H, J = 15.4 Hz), 7.15–7.19 (m, 1H), 7.22–7.25 (m, 4H), 7.40 (d, 2H, J = 8.0 Hz), 7.77 (d, 2H, J = 8.0 Hz), 7.84 (s, 1H), 8.19 (s, 1H). ^{13}C-NMR (CD_3OD) δ: 21.5, 37.4, 41.5, 45.0, 54.4, 60.2, 62.4, 73.1, 127.6, 127.7, 128.0, 129.1, 130.7, 138.7, 140.7, 144.8, 156.4, 157.8, 160.8, 164.3.