Pergamon

Tetrahedron Letters 40 (1999) 9069–9072

TETRAHEDRON LETTERS

The first synthesis of a 2′,3′-methano carbocyclic nucleoside[1]

Nobuya Katagiri,* Yoshitsugu Yamatoya and Minoru Ishikura

Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido, Ishikari-Tobetsu, Hokkaido 061-0293, Japan

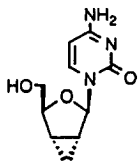
Received 6 September 1999; revised 29 September 1999; accepted 1 October 1999

Abstract

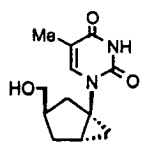
A 2′,3′-methano carbocyclic nucleoside, 9-(*c*-4-hydroxymethylbicyclo[3.1.0]hex-*r*-2-yl)-9*H*-adenine, has been efficiently synthesized from 2-azabicyclo[2.2.1]hex-5-en-3-one(ABH) in six steps involving 1,3-dipolar cycloaddition, photolysis, and adenine ring construction.

Keywords: 2-azabicyclo[2.2.1]hept-5-en-3-one; diazomethane; photolysis; 2′,3′-methano carbocyclic nucleoside.

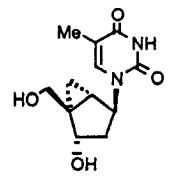
A cyclopropane fused nucleoside, namely methano-nucleoside, has recently attract much attention because of its pharmacological and biological activities. A methano cytidine derivative (**A**) shows antiviral activity.[2] Three types of methano carbocyclic nucleosides (**B**,[3] **C** and **D**) have been synthesized so far. Carbocyclic 4′,6′-methano- (**C**) and 1′,6′-methano-thymidine (**D**) assume 2′-*exo* and 3′-*exo* conformations, respectively. The nucleoside (**C**) shows significant anti-HSV activity[4] and the oligomer containing **C** has been found to stabilized the duplex.[5] The oligomer consisting of **D** also forms the duplex with the complemental natural oligomer.[6] Quite recently, a cyclopentenyl guanine derivative (**E**: carbovir) has been approved as a drug for the treatment of AIDS.[7] Previously, we reported an efficient synthesis of a precursor of abacavir from 2-azabicyclo[2.2.1]hept-5-en-3-one (ABH) via π-allylpalladium complex.[8] We planned to design a methano derivative (**F**) because a cyclopropane ring as well as a C–C double bond has unsaturated property and therefore **F** can be expected to show anti-HIV activity. In this communication, we now report the first synthesis of racemic **F** from ABH.



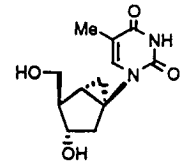
A



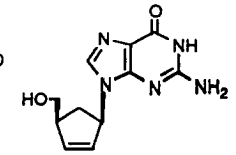
B



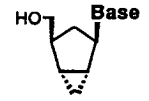
C



D



E (carbovir)



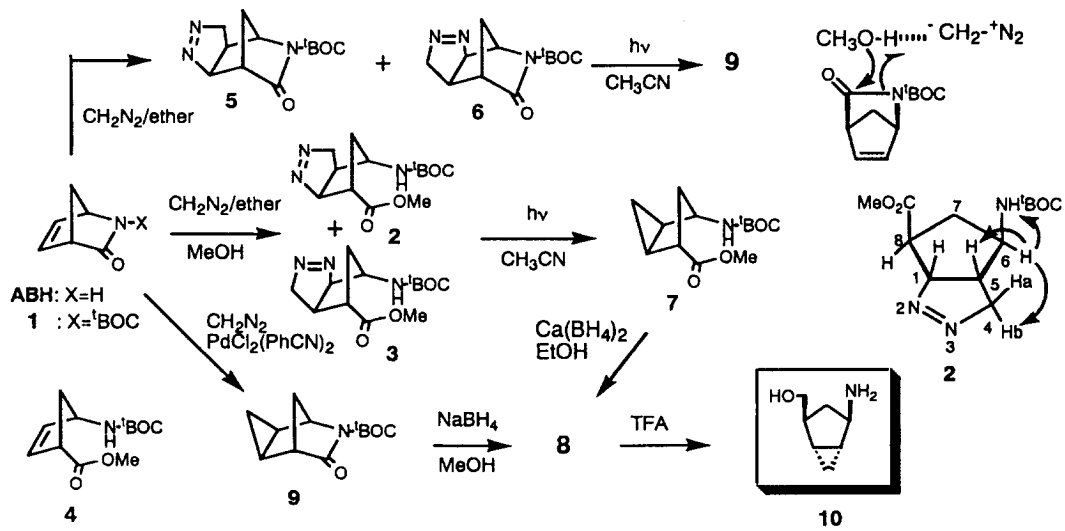
F

Cyclopropane construction was carried out using diazomethane because Simmons–Smith reaction of ABH or its *N*-ᵗBoc derivative (**1**)[9] did not give the desired compound.[10] When **1** was treated with an

* Corresponding author. Tel: +81 1332 3 1211 ext. 3100; fax: +81 1332 3 1245; e-mail: nobu@hoku-iryo-u.ac.jp

0040-4039/99/$ - see front matter
PII: S0040-4039(99)01910-3

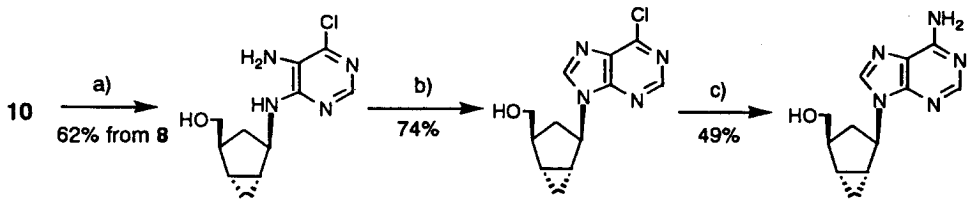
excess of diazomethane–ether solution[11] containing methanol at room temperature overnight, a mixture of **2**[12] and **3**[12] was obtained with the 1:1 ratio in 69% yield concomitant with the formation of **4** (20%). The structure of **2** was confirmed by NOE experiments as shown in Scheme 1. Since **4** did not react with diazomethane under the same conditions, compounds **2** and **3** would be formed by the 1,3-dipolar cycloaddition of **1** with diazomethane followed by solvolysis with methanol. The initial cycloaddition selectively occurred from the *exo* side of **1** in the same manner as the epoxidation of **1** by *m*-CPBA.[13] It is also proved by the latter mentioned reaction. Formation of **4** might be assisted by diazomethane (Scheme 1) because conversion of **1** to **4** did not take place in methanol under neutral condition.[14] Reaction of **1** with diazomethane in the absence of methanol[11] gave a mixture of regioisomers **5**[15] and **6**[15] in 58% and 35% yields, respectively. Determination of the structure of **5** and **6** was made by their conversion to **2** and **3**, respectively. Both compounds were readily converted to the corresponding bicyclo-compound **2** and **3** by methanolysis at room temperature for 10 min. Although **2** and **3** were chromatographically separable, the mixture was used for the following reaction without separation. Thus, a solution of the mixture in acetonitrile was irradiated with high pressure marcury lamp (Pyrex filter) with ice-cooling for 2 h to give a cyclopropane derivative (**7**) in 94% yield. Reduction of **7** with $Ca(BH_4)_2$ in ethanol afforded an alcohol (**8**)[16] in 81% yield.



Scheme 1.

A more straightforward synthesis of **8** was examined. Compound (**1**) was treated with diazomethane–ether solution without methanol in the presence of $PdCl_2(PhCN)_2$ to give directly a tricyclic compound (**9**) in 41% yield, which was consistent with the compound obtained from the photolysis of **5** and **6** in 42% and 60% respective yields. Compound (**9**) was then submitted to reductive amido cleavage (RAC) reaction using $NaBH_4$ developed previously by our group[17] to form **8** in 70% yield. Cyclopropanation of **4** with diazomethane using transition metal catalysts was also investigated to obtain **7** directly. Use of $PdCl_2(PhCN)_2$ resulted in the formation of **7** in low yield (23%) whereas $Rh_2(OAc)_2$ did not catalyze the reaction. Removal of the ^{t}Boc group of **8** with trifluoroacetic acid (TFA) gave the desired product (**10**), which, without purification, was submitted to the manipulation of adenine ring construction to give the final product (**13**)[18] via **11** and **12** as shown in Scheme 2.

In conclusion, we have achieved the first synthesis of 2′,3′-methano carbocyclic nucleoside (**13**) from ABH in ca. 12% total yield. We have found that **1** is more reactive than the cyclopentene (**4**) for both the



Scheme 2. (a) 5-Amino-4,6-dichloropyrimidine, *i*-Pr_2NEt, *n*-BuOH, reflux, 24 h; (b) $CH(OEt)_3$, 10N HCl, rt, 20 h; (c) NH_3, MeOH, 50°C, 24 h (sealed tube)

1,3-dipolar cycloaddition with diazomethane and the cyclopropanation using $PdCl_2(PhCN)_2$. This might be attributable to factor 'X'[19] or staggering of allylic bond[20] as observed in the cycloaddition to the C=C bond of norbornene. Works on the antiviral evaluation of **13** and the synthesis of its guanine congener are in progress, and the results will be reported in due course.

Acknowledgements

We wish to thank Kuraray Co., Ltd for providing us 2-azabicyclo[2.2.1]hept-5-en-3-one (ABH).

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12. Compound **2** (less polar): mp 123°C (dec.) (hexane–AcOEt). ^1H NMR (400 MHz, $CDCl_3$): 1.43 (9H, s), 1.80 (1H, dt, J=13.7, 8.4 Hz), 1.92 (1H, dt, J=13.7, 5.1 Hz), 2.40 (1H, br s), 3.35 (1H, br s), 3.58 (1H, br s), 3.82 (3H, s), 4.55 (1H, dd, J=18.6, 9.0 Hz), 4.70 (1H, dt, J=18.6, 2.9 Hz), 5.11 (1H, br s), 5.30 (1H, ddd, *J*=8.3, 5.4, 2.9 Hz). **3** (more polar): ^1H NMR (300 MHz, $CDCl_3$): 1.48 (9H, s), 1.92 (2H, m), 2.31 (1H, dd, J=6.3, 2.7 Hz), 2.83 (1H, m), 3.72 (3H, s), 4.39 (1H, dd, J=18.3, 8.4 Hz), 4.44 (1H, br s), 4.66 (1H, d, J=18.4 Hz), 4.93 (1H, br s), 5.41 (1H, br s).
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14. Compound **4** was prepared in 54% yield by refluxing of **1** in methanol with catalytic amount of conc. hydrochloric acid for 4 h, mp 36°C.

15. Compound **5** (less polar): mp 143°C. ^{1}H NMR (300 MHz, $CDCl_3$): 0.83 (1H, br d, J=11.3 Hz), 1.58 (9H, s), 1.85 (1H, dt, J=11.3, 1.5 Hz), 2.51–2.61 (1H, m), 2.63 (1H, br s), 4.23 (1H, dt, J=19.0, 3.4 Hz), 4.71 (1H, ddd, J=19.0, 9.7, 1.7 Hz), 5.06 (1H, t, J=1.5 Hz), 5.29–5.36 (1H, m). **6** (more polar): mp 148–150°C. ^{1}H NMR (300 MHz, $CDCl_3$): 0.83 (1H, br d, J=11.4 Hz), 1.53 (9H, s), 1.86 (1H, br d, J=11.4 Hz), 2.54–2.65 (1H, m), 3.47 (1H, br s), 4.23 (1H, dt, J=19.0, 4.2 Hz), 4.29 (1H, br s), 4.59 (1H, ddd, J=19.0, 9.8, 1.5 Hz), 5.28 (1H, br dd, J=7.1, 1.1 Hz).
16. ^{1}H NMR (400 MHz, $CDCl_3$): 0.00 (1H, m, overlapped with TMS), 0.49 (1H, dt, J=8.3, 5.4 Hz), 1.34 (2H, m), 1.44 (10H, s and m), 1.78 (1H, dt, J=14.6, 7.3 Hz), 2.16 (1H, dt, J=8.8, 4.4 Hz), 2.80 (1H, br), 3.58 (1H, dd, J=10.3, 4.4 Hz), 3.70 (1H, dd, J=10.3, 3.9 Hz), 4.00 (1H, br), 5.90 (1H, d, NH).
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18. Compound **13**: mp 215–216°C. ^{1}H NMR (400 MHz, CD_3OD): 0.44 (1H, dt, J=4.9, 3.9 Hz), 0.88 (1H, dt, J=5.3, 8.4 Hz), 1.81 (1H, dt, J=8.3, 4.4 Hz), 1.94 (1H, dt, J=8.3, 3.9 Hz), 2.07 (1H, dt, J=15.6, 7.8 Hz), 2.28 (1H, q, J=7.8 Hz), 3.18 (1H, dd, J=10.8, 7.8 Hz), 3.37 (1H, dd, J=10.8, 7.3 Hz), 4.91 (1H, d, J=6.8 Hz), 8.20 (1H, s), 8.36 (1H, s). Anal. calcd for $C_{12}H_{13}N_5O$: C, 59.25; H, 5.39; N, 28.79. Found: C, 59.15; H, 5.50; N, 28.63.
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