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A Highly Efficient Synthesis of the Antiviral Agent (+)-Cyclaradine Involving the Regioselective Cleavage of Epoxide by Neighboring Participation[1]

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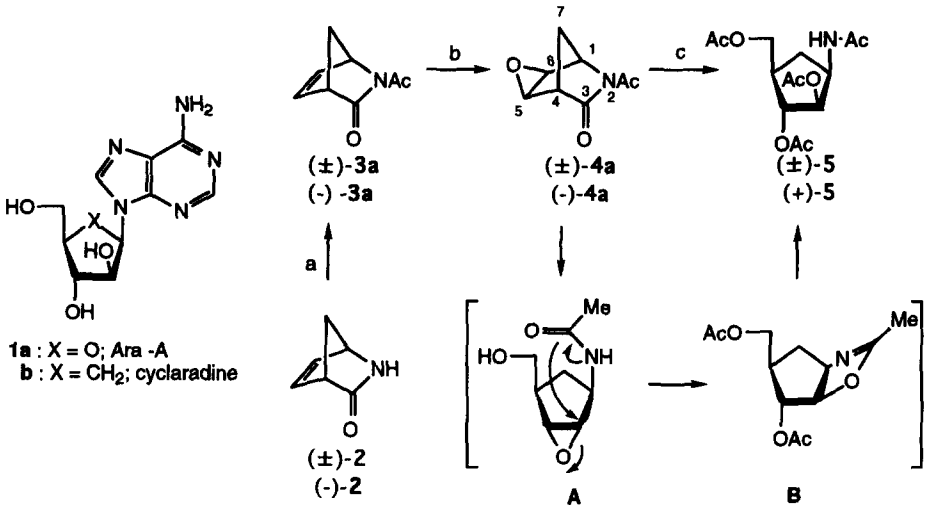
Abstract: (+)-Cyclaradine, carbocyclic arabinofuranosyladenine having anti-HSV activity, has been synthesized from (-)-2-azabicyclo[2.2.1]hept-5-en-3-one in only seven steps. The method involves the novel ring cleavage of epoxide by neighboring participation. © 1997 Elsevier Science Ltd. All rights reserved.

The finding that modified nucleosides such as carbocyclic nucleosides are potentially effective therapeutic agents for the treatment of viral diseases has triggered explosive new development in the chemistry of these compounds and their analogs.[2] Ara-A (**1a**: 9-β-D-arabinofuranosyladenine) has broad spectrum activity against DNA virus including HSV (herpes simplex virus).[3] However, a major drawback in the clinical use of Ara-A lies in the fact that the nucleoside is rapidly deaminated by adenosine deaminase to form Ara-H (9-β-D-arabinofuranosylhypoxanthine) which is considerably less active than Ara-A.[4] Therefore, Ara-A is used in the treatment of HSV infection only as a drug for external use. To overcome the deamination problem, cyclaradine (**1b**), carbocyclic arabinosyladenine , was developed by Vince and his coworkers as an adenosine deaminase-resistant Ara-A derivative.[5] Although some literature is available concerning the synthesis of **1b**,[5,6] the time-consuming reaction steps in all of these methods, resulting in low total yield, are disadvantageous.

In this communication, we report a highly efficient synthesis of **1b** from 2-azabicyclo[2.2.1]hept-5-en-3-one (**2**),[7] which is industrially produced. Our method involves the following essential features: 1) the stereo-controlled epoxidation of bicyclic amides (**3**), 2) the reductive amido-bond cleavage reaction (RAC reaction) by $NaBH_4$ previously reported in our laboratory,[8] and 3) the regioselective cleavage of the epoxide by neighboring participation.

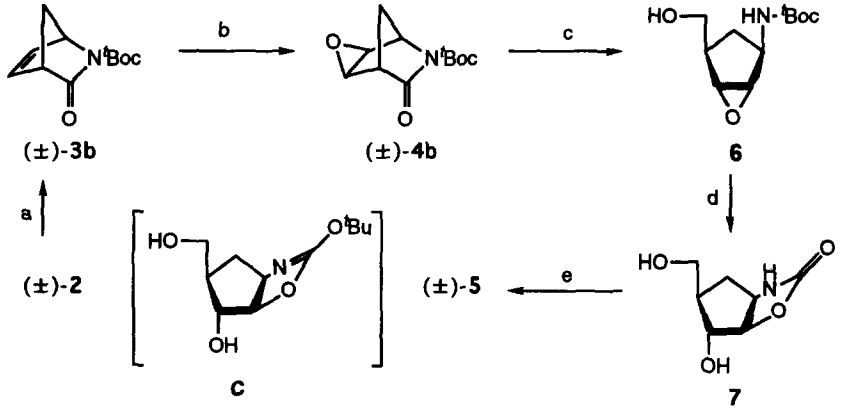
Not only to facilitate the RAC reaction but also to induce neighboring participation, the acetyl group as an electron-withdrawing group was introduced to the 2-position of (±)-(**2**). When (±)-**2** was acetylated with acetic anhydride in the presence of Et_3N-DMAP at room temperature for 4 h, the N-acetyl bicyclic amide (±)-**3a** was obtained as an oil (bp 60-61°C/0.1 mmHg) in 78% yield. Epoxidation of (±)-**3a** with *m*-CPBA in $CHCl_3$ occurred from the exo side to afford the epoxide (±)-**4a** (mp 61-63 °C)[9] as the sole product in 68% yield. The exo structure of epoxide (±)-**4a** was confirmed by later reactions. Thus, the epoxide (±)-**4a** was then subjected to the RAC reaction using $NaBH_4$, followed by acetylation to give the carbocyclic arabinofuranosylamine tetraacetate (±)-**5** (mp 137-138 °C, *lit.*[5a] mp 137-137.5 °C) in 63% yield. The mechanism for the formation of (±)-**5** from (±)-**4a** can be considered to be as follows: (±)-**4a**, on treatment with $NaBH_4$, undergoes the RAC



Scheme 1. Reagents and conditions: a) Ac_2O, Et_3N - DMAP, $CHCl_3$, r. t., 4 h; b) *m* – CPBA, $CHCl_3$, r. t., 72 h; c) 1) $NaBH_4$, MeOH, 30 min, 2) Ac_2O, pyridine, 1 h.

reaction to give the intermediate **A**, which is transformed to (±)-**5** *via* the oxazoline intermediate **B** formed by the neighboring participation of the acetylamino group. Employing the same procedure, the chiral (+)-**5**[10] was obtained from (-)-**2**[11]*via* (-)-**3a**[13] and (-)-**4a**[14].

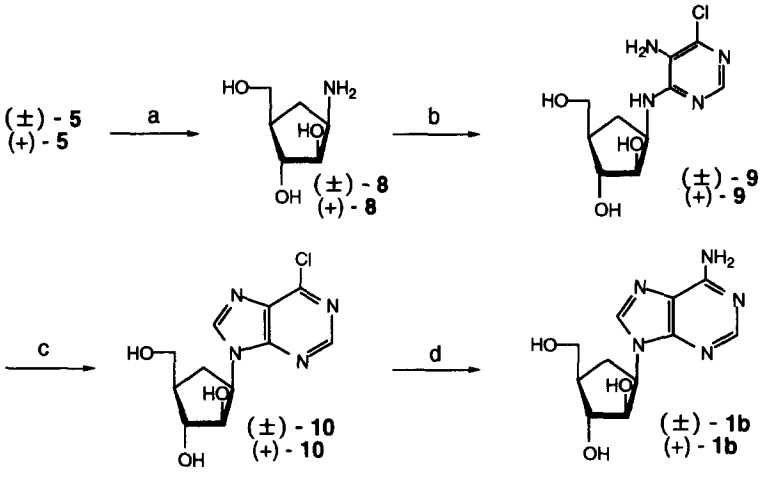
The transformation of N-*t*-Boc derivative (±)-**4b** to (±)-**5** was also examined. According to the procedure previously reported,[15] (±)-**3b** was obtained from (±)-**2** in 95% yield. Compound (±)-**3b** was then treated with *m*-CPBA to give the epoxide (±)-**4b** (mp123-125 °C) as the sole product in 75% yield. Compound (±)-**4b** was subjected to the RAC reaction to give the cyclopentane derivative **6** (mp 118-119 °C) in 85% yield.



Scheme 2. Reagents and conditions : a) $(CO_2{}^tBu)_2O$, Et_3N - DMAP, $CHCl_3$, r. t., 5 h; b) *m* - CPBA, $CHCl_3$, r. t., 48 h; c) $NaBH_4$, MeOH, 0 °C, 30 min; d) BF_3 - Et_2O, MeCN, r. t., 4 h; e) 1) 10 % KOH, MeOH, 70 °C, 2 h, 2) Ac_2O, pyridine, r. t., 1 h.

To open the epoxide ring, **6** was treated with BF_3-Et_2O in CH_3CN at room temperature to give **7** (mp 129-130 °C) in 92% yield, which would be formed *via* the intermediate **C** corresponding to **B** (in Scheme 1). Therefore, this reaction may be further substantiation of the mechanism for the formation of **5** from **4**. Compound **7** was hydrolyzed with 10% KOH-MeOH followed by acetylation to give (±)-**5** in 51% overall yield from **7**.

Next, the synthesis of **1b** from **5** was performed by the conventional purine ring construction. On acidic hydrolysis with 2*N* HCl followed by treatment with ion-exchange resin (Dowex 1-X8), (±)-**5** was converted to the amine (±)-**8**, which, without isolation, reacted with 5-amino-4,6-dichloropyrimidine to produce (±)-**9** in 78% yield. The ring closure of (±)-**9** with triethyl orthoformate produced 6-chloropurine derivative (±)-**10** in 70% yield. To prevent the formation of the 6-methoxypurine derivative, dioxane was.used as the solvent instead of MeOH for the amination of (±)-**10** to form the final product, racemic cyclaradine [(±)-**1b**](mp 265-267 °C, *lit.*[5a] 252.5-254.5 °C) in quantitative yield. In a similar manner, chiral (+)-**1b**[16] was also obtained from (+)-**5** *via* (+)-**8**, (+)-**9**, and (+)-**10**,[17] successively.



Scheme 3. Reagents and conditions: a) 2*N* HCl, 70 °C, 1 h; b) 5-amino-4,6-dichloropyrimidine, Et_3N, ^tBuOH, reflux, 18 h; c) $CH(OEt)_3$, 12*N* HCl, 12 h; d) NH_3, dioxane, 80 °C, 20 h.

In summary, we have achieved a highly efficient synthesis of **1b** from 2-azabicyclo[2.2.1]hept-5-en-3-one (**2**) in only seven steps, which is the shortest processes among the synthetic methods previously reported. The method involves a selective cleavage of the epoxide ring by means of neighboring participation of acylamino groups.[18] This cleavage reaction seems to be widely applicable to the regio- and stereo-selective synthesis of other carbocyclic nucleosides containing various functional groups (*e.g.*, amino function) at the 3-position. Study on the synthesis of these nucleosides is also in progress and the results will be reported in due course.

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9. (±)-**4a**: ^{1}H-NMR ($CDCl_3$)δ: 1.65 (1H, m, 7-H), 1.82 (1H, m, 7-H), 2.42 (3H, s, CH_3CO), 3.12 (1H, m, 4-H), 3.62 (1H, dd, J=4.0, 1.5 Hz, 5- or 6-H), 3.75 (1H, dd, J=4.0, 1.5 Hz, 5- or 6-H), 4.97 (1H, m, 1-H).
10. (+)-**5**: mp 125-126.5 °C, $[\alpha]_D^{23}$ + 40° (*c*=1.0, $CHCl_3$).
11. (-)-**2** was provided by Kuraray Co., Ltd., $[\alpha]_D^{26}$ -602° (*c*=1.1, $CHCl_3$) (*lit.*[12] $[\alpha]_D^{20}$ - 568°±15).
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13. (-)-**3a**: purified by column chromatography, $[\alpha]_D^{21}$ - 162° (*c*=1.0, $CHCl_3$).
14. (-)-**4a**: mp 70-71 °C, $[\alpha]_D^{22}$ - 62° (*c*=1.0, $CHCl_3$).
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16. (+)-**1b**: mp 258-260 (dec.) $[\alpha]_D^{25}$ +44° (*c*=1.0, MeOH) (*lit.*[6b] mp 235-245 °C, $[\alpha]_D^{20}$ +48° (*c*=1.5, MeOH)).
17. (+)-**10**: mp 152-153 °C, $[\alpha]_D^{19}$ + 62° (*c*=1.0, CHCl3).
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