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An efficient synthesis of the 4'-epimer of 2-fluoronoraristeromycin

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Abstract

The 4'-epimer of 2-fluoronoraristeromycin was synthesized by employing bis-*t*-butoxycarbonyl (Boc) protected 2-fluoroadenine as a superior substrate for the Mitsunobu reaction with the appropriate cyclopentenol. Unlike the unsubstituted counterpart 2-fluoroadenine, this substrate is completely soluble in THF and resulted in a very good yield in the Mitsunobu coupling reaction as well as subsequent steps.

Keywords

Malaria; Carbocyclic nucleosides; 2-Fluoronoraristeromycin; S-adenosyl-L-homocysteine hydrolase

Introduction

The antiviral activity of carbocyclic nucleosides such as aristeromycin and neplanocin A (Fig. 1) is attributed to the inhibition of S-adenosyl-L-homocysteine hydrolase (SAHH), a hydrolytic enzyme that catalyzes the breakdown of S-adenosyl-L-homocysteine (SAH) to give adenosine and homocysteine.¹ SAH is a biofeedback inhibitor of methyltransferases, enzymes that catalyze essential biological methylation reactions. Therefore, inhibition of the enzyme that removes S-adenosyl-L-homocysteine, namely SAHH, increases the cellular level of SAH resulting in the suppression of methylation reactions.

Recently, *Plasmodium falciparum*, the causative agent of malaria, has been shown to possess a specific S-adenosyl-L-homocysteine hydrolase (PfSAHH).² X-ray crystal structure analysis of PfSAHH complexed with adenosine has revealed that there is a crucial structural difference between PfSAHH and the human (*Homo sapiens*) S-adenosyl-L-homocysteine hydrolase (HsSAHH).³ The active site of PfSAHH has an extra space located near the C2 of

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adenine ring (not present in HsSAHH) suggesting that substitution of the hydrogen of C2 by a functional group of the right size would fill the space and enhance selective inhibition of PfSAHH.⁴

Noraristeromycin (**1**), a carbocyclic nucleoside lacking the methylene group of aristeromycin (Fig. 2), possesses a significant inhibitory activity against PfSAHH (IC_{50} = 3.1 μ M) although it is not selective (selectivity index = mean IC_{50} for HsSAHH/mean IC_{50} for PfSAHH = 0.35).⁵ On the other hand, 2-fluoronoraristeromycin (**2**) is less potent (IC_{50} for PfSAHH = 13 μ M) than the parent compound **1**, however, the introduction of fluorine at the 2-position of the adenine ring clearly confers selectivity (selectivity index = 4.8) as expected based on the structural differences at the active site of the hydrolases of the parasite (PfSAHH) and the host (HsSAHH).⁶ Another important observation in this class of compounds is that **3**, the 4'-epimer of noraristeromycin, showed even better selectivity (selectivity index 9.6) than both noraristeromycin and its 2-fluoro analogue.⁷

In our pursuit of carbocyclic nucleosides with improved antimalarial activity and selectivity, we sought compound **4**, (the 4'-epimer of 2-fluoronoraristeromycin) since it combines a 2-fluoro substituent and an α face 4'-hydroxyl group, features that led to improved selectivity in the lead compounds **2** and **3**. An efficient and facile synthesis of **4** is reported here.

Chemistry

Mitsunobu reaction, which is widely used in the preparation of carbocyclic nucleosides, could be employed to couple 2-fluoroadenine and the requisite substituted cyclopentenol at the beginning of a convergent approach to the target compound.⁸ However, the yield of this reaction is severely hampered by the extremely low solubility of 2-fluoroadenine under typical Mitsunobu condition (THF, PPh_3 , DIAD). In our hands, the yield of this reaction never exceeded 27%.

Recently, it was shown that bis-*t*-butoxycarbonyl (Boc) protected adenine couples with a variety of substituted cyclopentan(en)ols in the Mitsunobu reaction at room temperature with yields ranging from 85–96% in conveniently short reaction times.⁹ In order to extend this observation to the preparation of **4**, bis-Boc-2-fluoroadenine was prepared as shown in scheme 1. Reaction of 2-fluoroadenine with di-*tert*-butyl dicarbonate (Boc_2O) in the presence of catalytic amount of 4-dimethylaminopyridine (DMAP) afforded tris-Boc substituted derivative **6**.¹⁰ Removal of the N-9 Boc group was achieved using saturated sodium bicarbonate in methanol resulting in **7**.

Next, the allylic alcohol **8**¹¹ was subjected to Mitsunobu reaction in the presence of bis-Boc-2-fluoroadenine to give the coupling product **9** (Scheme 2). Unlike the Mitsunobu reaction involving the unprotected 2-fluoroadenine, the bis-Boc protected derivative proved to be a superior substrate in that it is completely soluble in THF and the reaction was completed in 4 h at room temperature (yield 88 %). This was followed by dihydroxylation of **9** using 4-methylmorpholine *N*-oxide and catalytic amount of osmium tetroxide to yield the diol **10**. The *t*-butoxycarbonyl group was then removed by a 1:1 mixture of trifluoroacetic acid and dichloromethane at room temperature.¹² The synthesis of the target compound was completed with the deacetylation of **11** using ammonia gas in methanol.

Conclusion

An efficient preparation of the 4'-epimer of 2-fluoronoraristeromycin has been achieved via Mitsunobu coupling of an allylic cyclopentenol and bis-Boc-2-fluoroadenine. This convenient and high yielding reaction points to the extremely desirable properties of bis-

Boc-2-fluoroadenine as an excellent substrate for Mitsunobu reactions in the synthesis of biologically important fluorinated carbocyclic nucleosides. A study of the antimalarial properties of the target compound will be forthcoming.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Biologically active carbocyclic nucleosides

- 1** R = H, Noraristeromycin
2 R = F, 2-Fluoronoraristeromycin

- 3** R = H, 4'-Epimer of noraristeromycin
4 R = F, 4'-Epimer of 2-fluoronoraristeromycin

Figure 2.
Lead and target compounds

Scheme 1.
Preparation of **7**

Scheme 2.
Preparation 4