



Synthesis of the 6'-iso analogues of neplanocin A and 5'-homoneplanocin A

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ARTICLE INFO

Article history:

Received 11 September 2009

Revised 1 October 2009

Accepted 2 October 2009

Available online 8 October 2009

Keywords:

Carbocyclic nucleosides

Grubbs reaction

Mitsunobu reaction

ABSTRACT

An efficient synthesis of 6'-isoneplanocin A and 6'-isohomoneplanocin A is reported. The key steps in the synthesis include an enyne metathesis and a regioselective oxidation.

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1. Introduction

Inhibition of *S*-adenosyl-L-homocysteine hydrolase (AdoHcy hydrolase) has been recognized as an important approach to develop new antiviral agents¹. As one of the most potent inhibitors of AdoHcy hydrolase, the naturally occurring carbocyclic nucleoside neplanocin A (**1**) has shown significant broad antiviral activities.² However, this antiviral potential is limited by its toxicity as a result of phosphorylation of the C-5' primary hydroxyl group.³ In seeking ways to circumvent this undesirable transformation, 5'-homoneplanocin A (**2**) with a C-5'-extended side-chain was synthesized and found to have significant activity against HBV and HCV without associated toxicity.⁴ Other C-5' neplanocin A modifications have considered adding a methyl group to enhance the steric interference to phosphorylation at this site⁵ and removal of the C-5' hydroxyl or

C-4' hydroxymethyl substituents.⁶ Apio-neplanocin A **3**⁷ and apio-homoneplanocin A **4**,⁸ which are the C-3' isomers of **1** and **2**, have been reported. While failing to inhibit AdoHcy hydrolase, **3** was found to have biological activity as a potent, selective A₃ adenosine receptor agonist.^{7b} The failure of **3** and **4** to inhibit the hydrolase could be the consequence of their C-3'-tertiary center⁹ (Fig. 1).

In our pursuit of neplanocin A analogues with non-toxic, antiviral potential, the 6'-iso analogues **5** and **6** emerged as worthy targets. An enantiomerically efficient preparation of the 6'-isoneplanocin A analogues **5** and **6** from *D*-ribose is reported here.

2. Results

The synthesis began with the protected glycol enal **7**,¹⁰ which can be prepared in large scale from inexpensive *D*-ribose in two steps

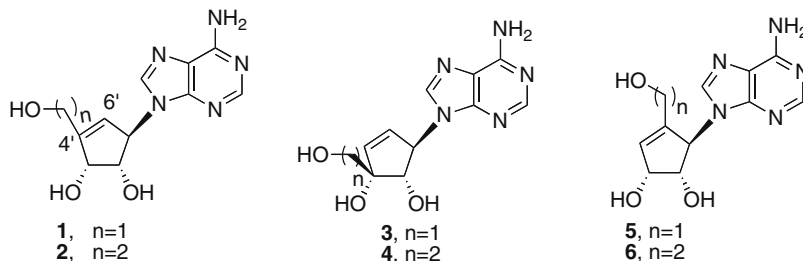
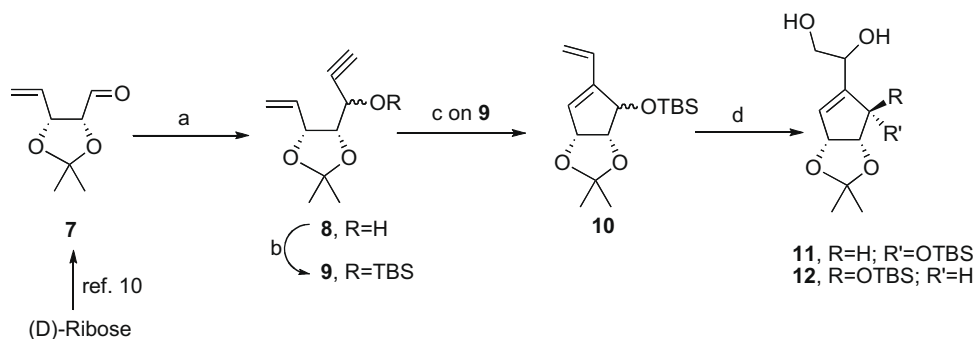
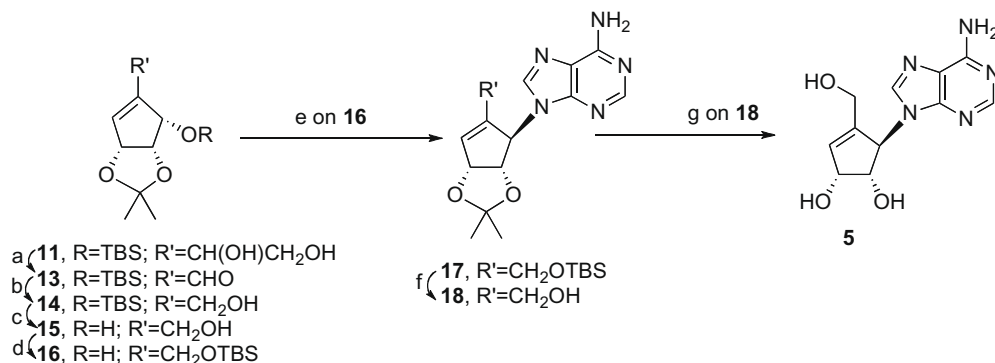


Figure 1. Neplanocin A and related analogues.

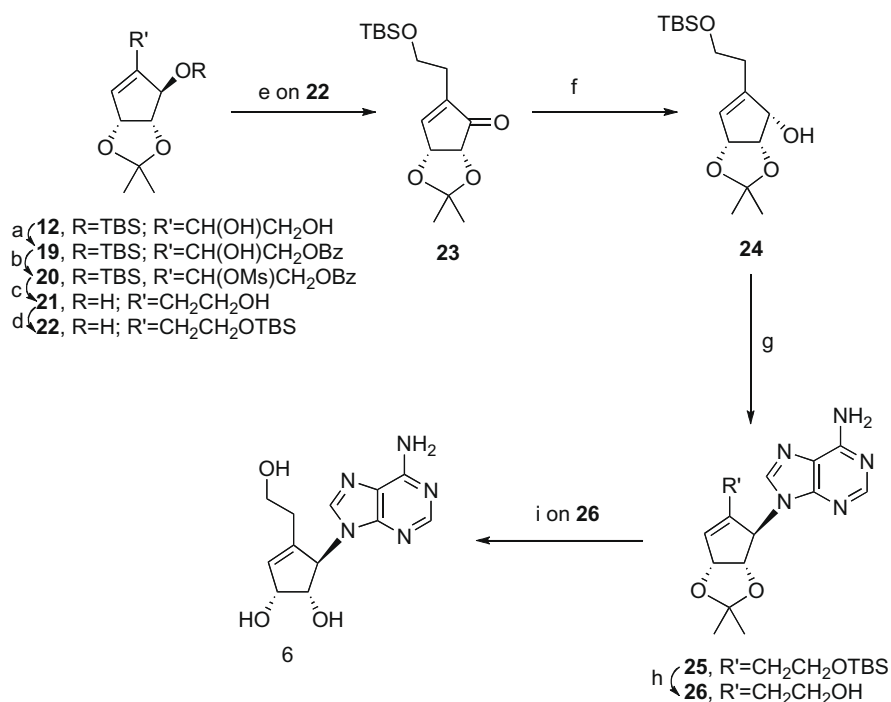
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Scheme 1. Reagents and conditions: (a) $\text{HC}\equiv\text{CMgBr}$, THF, 86%; (b) TBSCl, imidazole, CH_2Cl_2 , 83%; (c) first generation Grubbs catalyst, ethylene, CH_2Cl_2 , 86%; (d) AD-mix- α , t -BuOH/ H_2O , 83%.



Scheme 2. Reagents and conditions: (a) NaIO_4 , MeOH/ H_2O , 92%; (b) NaBH_4 , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, MeOH, 92%; (c) TBAF, THF; (d) TBSCl, imidazole, CH_2Cl_2 , 82% in two steps from **14**; (e) DIAD, PPh₃, 1 equiv adenine, THF; (f) TBAF, THF, 46% in two steps from **16**; (g) HCl, MeOH, 94%.



Scheme 3. Reagents and conditions: (a) BzCl , Et_3N , CH_2Cl_2 , 97%; (b) MsCl , Et_3N , CH_2Cl_2 ; (c) LiAlH_4 , THF, 72% in two steps; (d) TBSCl, imidazole, CH_2Cl_2 , 97%; (e) IBX, EtOAc; (f) NaBH_4 , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, MeOH, 86% in two steps from **22**; (g) DIAD, PPh₃, 1 equiv adenine, THF; (h) TBAF, THF, 43% in two steps from **24**; (i) HCl, MeOH, 91%.

(Scheme 1). Ethynylmagnesium bromide addition to **7** gave enyne **8**, which was protected as its *tert*-butyldimethylsilyl derivative **9**. An enyne metathesis¹¹ of substrate **9** gave product **10** in excellent yield.

The α - and β -isomers of **10** could not be separated at this stage and were used directly in the next step. Taking advantage of the different reaction rates between a terminal alkene and an internal one in the

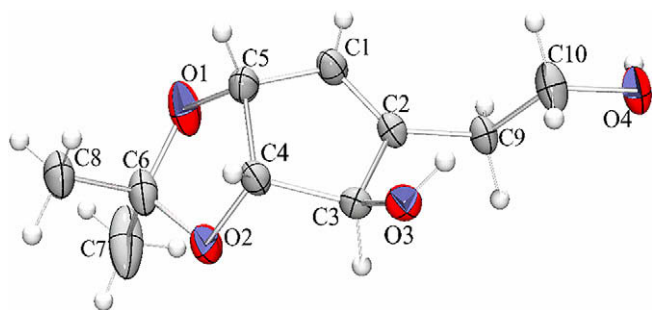


Figure 2. X-ray structure of **21**.

Sharpless asymmetric dihydroxylation,¹² the highly regioselective products **11** and **12** were achieved by treating **10** with AD-mix- α in the absence of methanesulfonamide. The two isomers (α and β) were easily isolated by flash column chromatography and the ratio of α isomer to β isomer was ca. 4:5.¹³ The α isomer **11** was then chosen to synthesize neplanocin A analogue **5** while the β isomer **12** was selected for homoneplanocin A analogue **6**.

Oxidative cleavage of **11** (to **13**) (Scheme 2) followed by reduction using Luche reagent produced **14**. Removal of the TBS group of **14** with TBAF (to **15**) and selective protection of the primary hydroxyl group with TBS yielded **16**. The Mitsunobu coupling⁴ of **16** with 1 equiv of adenine¹⁴ (to **17**) followed by desilylation afforded **18**. The target compound 6'-isoneplanocin A (**5**)¹⁵ was achieved by removal of the isopropylidene of **18** under acidic conditions.

To achieve **6** (Scheme 3), the primary alcohol of **12** was first benzoylated (to **19**) that was followed by mesylation to **20**. Reduction of **20** using lithium aluminum hydride removed the mesyl, benzoyl, and TBS groups to afford diol **21**, whose crystal structure (Fig. 2) was obtained (which further supported the previous stereochemical assignment of **11** and **12**).¹⁶ The primary hydroxyl of **21** was selectively protected with a TBS group. Because of difficulties using Mitsunobu conditions to invert the allylic hydroxyl group of **22**, an oxidation–reduction approach was selected. Thus, **22** was first oxidized using IBX (2-iodoxybenzoic acid) in refluxing EtOAc¹⁷ to afford enone **23**. This was followed by a Luche reduction to avail the desired α isomer **24**. Pursuing steps similar to the synthesis of **5**, Mitsunobu coupling⁴ of **24** with 1 equiv of adenine¹⁴ and followed by removal of hydroxyl protection completed the synthesis of **6**.¹⁸

In summary, an efficient pathway to the 6'-isoneplanocin A targets **5** and **6** has been developed. The antiviral data associated with this new class of carbocyclic nucleosides is forthcoming.

Acknowledgments

This research was supported by funds from Department of Health and Human Services (AI 56540). We thank Drs. Thomas Albrecht-Schmitt and John Gorden, Auburn University, for securing the X-ray data for **21**.

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 - The configuration of the protected allylic hydroxyl group was assigned by comparing the NMR spectrum of **11** with the Sharpless oxidation product of **10 α** (see below). For this purpose, **8 α** and **8 β** were readily separated by column chromatography and their structures assigned by ¹H NMR spectroscopy (i.e., Ha of **8 β** is a singlet while Ha of **8 α** is multiplet; Hb of **8 β** is a doublet while Hb of **8 α** is a triplet).
- 8 $\xrightarrow[\text{low conversion}]{\text{Grubbs 1st generation catalyst, ethylene, 3 days}}$ 8 β , R=OH; R'=H
8 α , R=H; R'=OH
10 α , R=H; R'=OTBS
- A** was observed when more than 1 equiv of adenine was used. However, **A** could be converted to **5** and **6** under the acidic deprotection.
- A $\xrightarrow{\text{HCl/MeOH}}$ 5, n=1
6, n=2
- Selected data for **5**: ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.09 (s, 1H), 8.06 (s, 1H), 7.21 (s, 2H), 5.92 (s, 1H), 5.33 (d, 1H, *J* = 5.6 Hz), 5.04 (m, 1H), 4.84 (m, 2H), 4.47 (m, 2H), 3.66 (m, 2H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 156.5, 152.8, 150.1, 145.2, 141.0, 129.1, 120.0, 76.4, 71.8, 65.4, 58.3. HRMS calcd for C₁₁H₁₃N₅O₃ 263.1018, found 263.1017.
 - Crystallographic data (excluding structure factors) for the structure in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 744708. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.
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 - Selected data for **6**: ¹H NMR (400 MHz, MeOD-*d*₄): δ 8.14 (s, 1H), 8.10 (s, 1H), 5.96 (s, 1H), 5.45 (m, 1H), 4.59 (m, 1H), 4.55 (m, 1H), 3.55 (m, 2H), 2.08 (m, 1H), 1.90 (m, 1H); ¹³C NMR (100 MHz, MeOD-*d*₄): δ 154.4, 150.8, 148.1, 141.3, 139.2, 128.6, 75.1, 70.5, 65.2, 57.6, 41.8, 30.0. HRMS calcd for C₁₂H₁₅N₅O₃ 277.1175, found 277.1182.