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

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ABSTRACT

An efficient synthesis of 6′-*iso*neplanocin A and 6′-*iso*homoneplanocin A is reported. The key steps in the synthesis include an enyne metathesis and a regioselective oxidation.

1. Introduction

Inhibition of *S*-adenosyl-L-homocysteine hydrolase (AdoHcy hydrolase) has been recognized as an important approach to develop new antiviral agents [1]. 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 site[5] 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 A_3 adenosine receptor agonist.[7b] The failure of **3** and **4** to inhibit the hydrolase could be the consequence of their C-3′-tertiary center[9] (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′-*iso*neplanocin 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

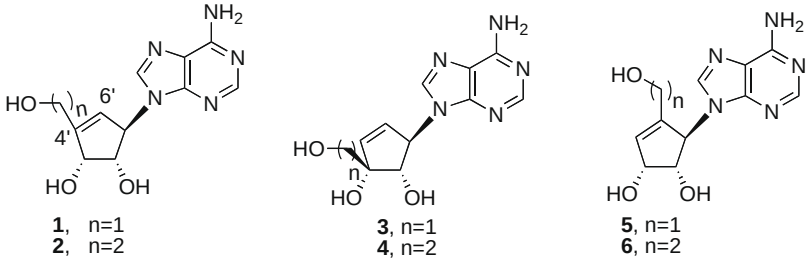

Figure 1. Neplanocin A and related analogues.

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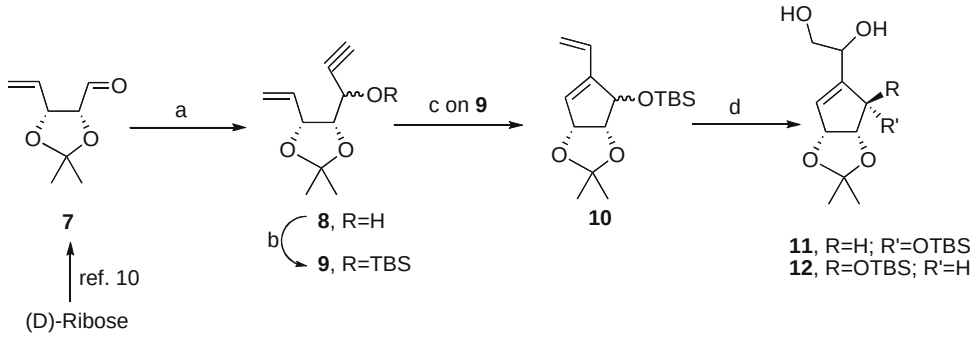
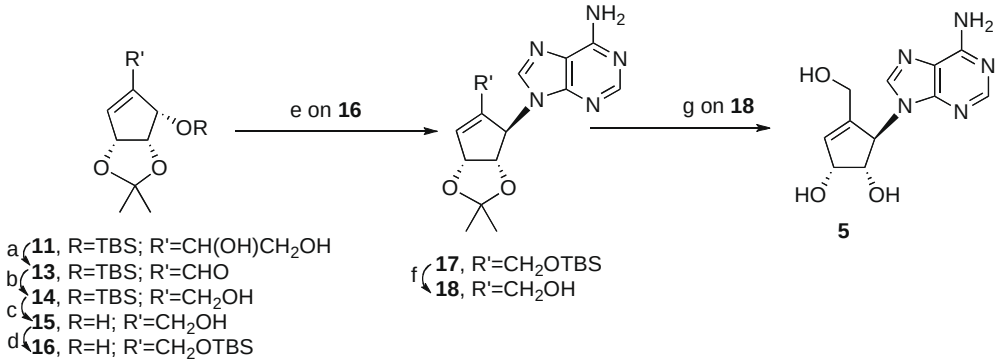
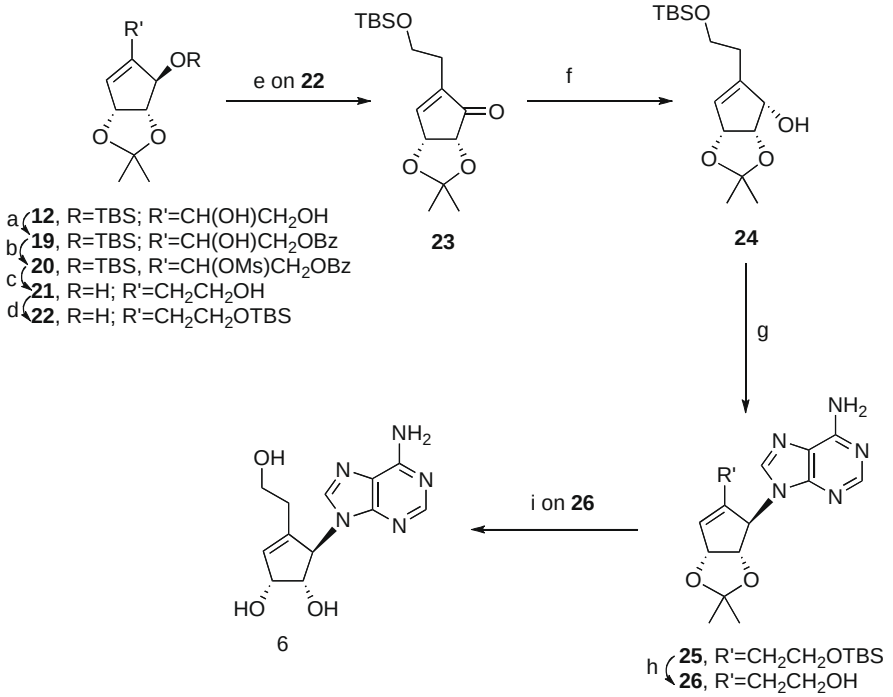


Scheme 1. Reagents and conditions: (a) HC≡CMgBr, THF, 86%; (b) TBSCl, imidazole, CH_2Cl_2, 83%; (c) first generation Grubbs catalyst, ethylene, CH_2Cl_2, 86%; (d) AD-mix-α, *t*-BuOH/H_2O, 83%.



Scheme 2. Reagents and conditions: (a) $NaIO_4$, MeOH/H_2O, 92%; (b) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 92%; (c) TBAF, THF; (d) TBSCl, imidazole, CH_2Cl_2, 82% in two steps from **14**; (e) DIAD, PPh_3, 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) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 86% in two steps from **22**; (g) DIAD, PPh_3, 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 metathesis[11] 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

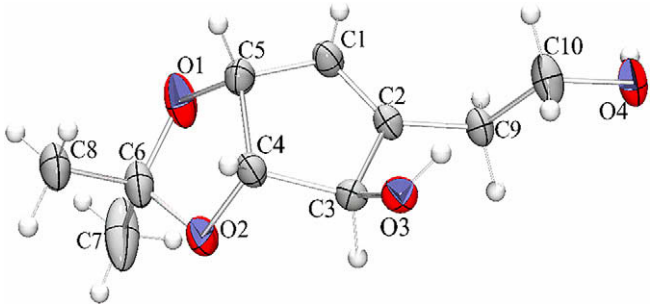


Figure 2. X-ray structure of **21**.

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 coupling[4] of **16** with 1 equiv of adenine[14] (to **17**) followed by desilylation afforded **18**. The target compound 6′-*iso*neplanocin A (**5**)[15] was achieved by removal of the *iso*propylidene 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 EtOAc[17] 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 coupling[4] of **24** with 1 equiv of adenine[14] and followed by removal of hydroxyl protection completed the synthesis of **6**.[18]

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

Acknowledgments

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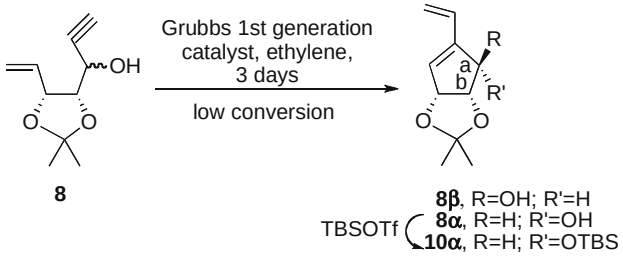
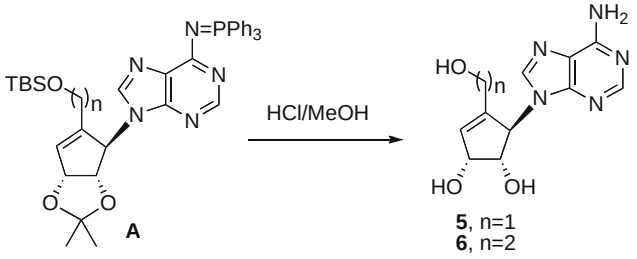
13. The configuration of the protected allylic hydroxyl group was assigned by comparing the NMR spectrum of **11** with the Sharpless oxidation product of **10α** (see below). For this purpose, **8α** and **8β** were readily separated by column chromatography and their structures assigned by ^{1}H NMR spectroscopy (i.e., Ha of **8β** is a singlet while Ha of **8α** is multiplet; Hb of **8β** is a doublet while Hb of **8α** is a triplet).



14. **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.



15. *Selected data for* **5**: ^{1}H 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); ^{13}C 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 $C_{11}H_{13}N_5O_3$ 263.1018, found 263.1017.
16. 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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18. *Selected data for* **6**: ^{1}H 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); ^{13}C 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 $C_{12}H_{15}N_5O_3$ 277.1175, found 277.1182.