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Chemoenzymatic Synthesis and Synthetic Application of Enantiopure Aminocyclopentenols: Total Synthesis of Carbocyclic (+)-Uracil Polyoxin C and Its α-Epimer

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Abstract: Carbocyclic uracil polyoxin C (+)-**2** and its α-epimer (−)-**3** were synthesized in an efficient fashion from *cis*-4-(*N*-*tert*-butylcarbamoyl)cyclopent-2-en-1-ol (±)-**7**. The synthesis incorporates a concise, inexpensive chemoenzymatic synthesis of enantiopure aminocyclopentenols, a Pd-(0)-catalyzed substitution reaction, and a mild reduction of an α-nitro ester by $TiCl_3$/sodium borohydride. Significantly, this process demonstrates the synthetic utility of the versatile enantiopure aminocyclopentenol building block (−)-**4**.

Prompted by naturally occurring carbocyclic nucleosides such as aristeromycin[1a] and neplanocin A[1b] (Figure 1), an impressive variety of unnatural carbocyclic nucleosides have been prepared in recent years that display intriguing biological activities.[2] In addition to their demonstrated utility as antiviral[3] and antitumor[4] agents, these compounds promise improved metabolic stability and decreased toxicity relative to their natural nucleoside counterparts.[5] Although considerable attention has been paid to derivatives such as AZT and carbovir,[6] which contain a 5′-hydroxymethyl substituent, comparatively little effort has been directed toward the synthesis of carbocyclic analogues of nucleosides containing an amino acid substituent at the 5′ position such as uracil polyoxin C, **1** (Figure 1).[7]

The polyoxins and closely related nikkomycins exhibit selective antifungal activity through inhibition of chitin synthase, thereby preventing fungal cell wall growth. As this enzyme is found only in fungi and some insects, these agents tend to be nontoxic to plants and mammals. The modest activity exhibited by the polyoxins and nikkomycins against human pathogens such as *C. albicans* may be due to their poor outer membrane transport and/or hydrolytic instability.[7] The latter suggests that improved activity might be observed through isosteric replacement of the furanyl oxygen with a methylene group.

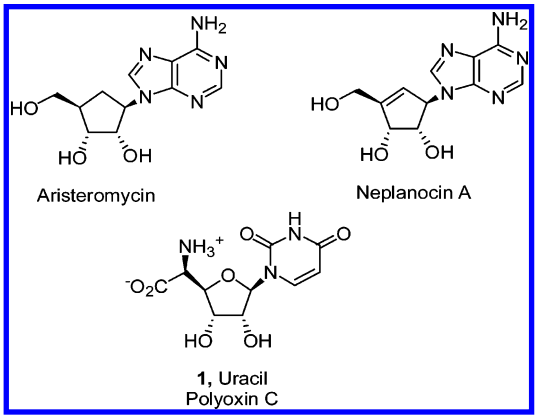

FIGURE 1. Structures of aristeromycin, neplanocin A, and uracil polyoxin C, **1**.

An impressive array of chemical[8] and chemoenzymatic[9] methods have been reported for the synthesis of carbocyclic nucleosides. Among these, cyclopentadiene-derived hetero- Diels−Alder cycloadducts[9g,10] such as **5** (Scheme 1) have emerged as particularly useful intermediates. A

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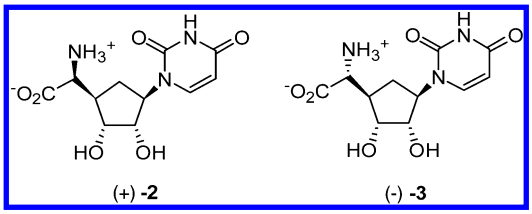
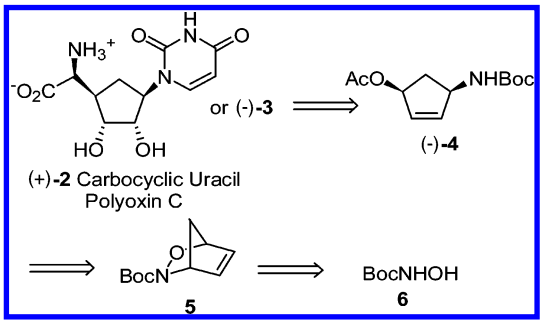


FIGURE 2. Target molecules.

SCHEME 1



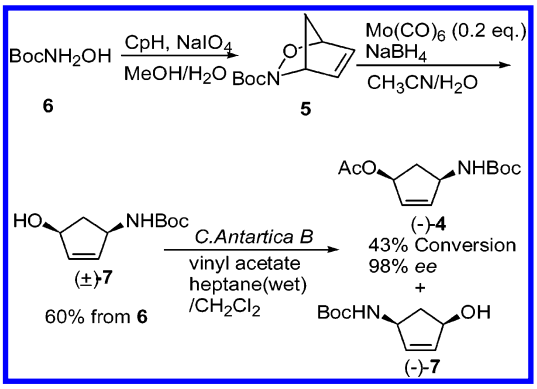
report from Cowart and co-workers[11] regarding the use of cycloadduct **5** for this purpose prompted us to disclose our most recent findings related to asymmetric syntheses of carbocyclic nucleosides from racemic **5**. We here report an efficient chemoenzymatic synthesis that provides the versatile synthetic intermediate (−)-**4** in 98% ee and in only two steps from racemic cycloadduct (±)-**5**. As part of an ongoing project, the utility of (−)-**4** was then demonstrated through the total synthesis of carbocyclic uracil polyoxin C (+)-**2** and its α-epimer (−)-**3** (Figure 2).

We previously reported application of cycloadduct (±)-**5** for the synthesis of racemic carbocyclic uracil polyoxin C (±)-**2**.[12] The success of our kinetic enzymatic resolution of aminocyclopentenols[13a] indicated (+)-**2** could now be readily prepared through unification of the two methods. In the process of completing this synthesis, substantial improvement over the existing methodology was realized including identification of a novel protocol for N−O reduction using substoichiometric $Mo(CO)_6$[13] in the presence of $NaBH_4$ and development of an efficient kinetic enzymatic resolution that provides the desired intermediate in good yield and in excellent enantiopurity (Scheme 2).

Careful optimization of the reduction step revealed that treatment of cycloadduct **(**±)-**5** with 0.2 equiv of molybdenum hexacarbonyl in the presence of excess sodium borohydride provided aminocyclopentenol (±)-**7** in 60% yield from **6**. Previously, reduction of (±)-**5** with 1.1 molar equiv of $Mo(CO)_6$ required a 2:1 $Mo(CO)_6$/substrate mass ratio.[13a] The use of less $Mo(CO)_6$ not only reduced the toxicity and cost of this synthetic transformation but also greatly simplified the purification process.

Initial studies have demonstrated that *Candida antarctica B* lipase accepts an allylic alcohol and provides (−)-**4** in two steps from **5** and in 80% ee.[13a] Recently, it

SCHEME 2



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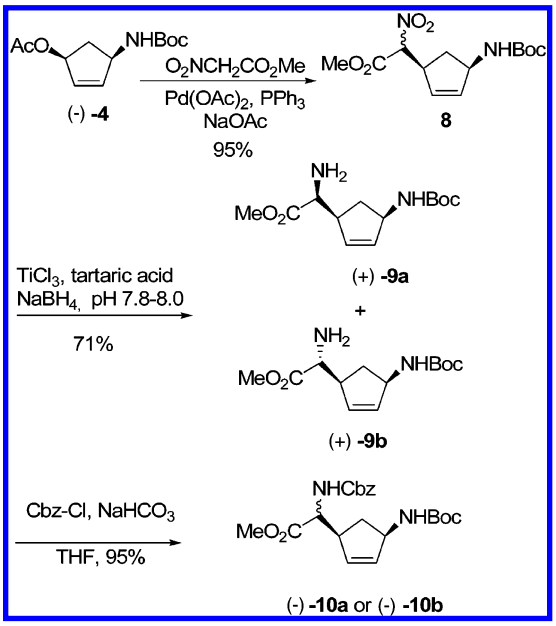

was discovered that use of commercially available immobilized *C. antartica B* enzyme resulted in dramatic improvement in substrate selectivity. Using this immobilized enzyme, the desired acetate (−)-**4** was obtained with 92−98% ee after 43% conversion, and this protocol worked well on a tens of grams scale. In addition to the outstanding efficiency observed using this new protocol, the resin-bound enzyme could be easily recovered from the reaction mixtures and reused in subsequent reactions.

With an efficient source for these useful intermediates, the asymmetric total syntheses of carbocyclic uracil polyoxin C (+)-**2** and its epimer (−)-**3** were initiated by introduction of the 5′-amino acid substituent masked as the nitroacetate using a stereospecific Pd(0)-mediated substitution reaction (Scheme 3).[14] The inseparable 1:1 mixture of diastereomeric nitroacetates was then reduced with $TiCl_3$ in the presence of sodium borohydride,[12] and the resulting diastereomeric aminoesters were separated by chromatography. The intermediate amines were individually treated with Cbz-chloride and sodium bicar-

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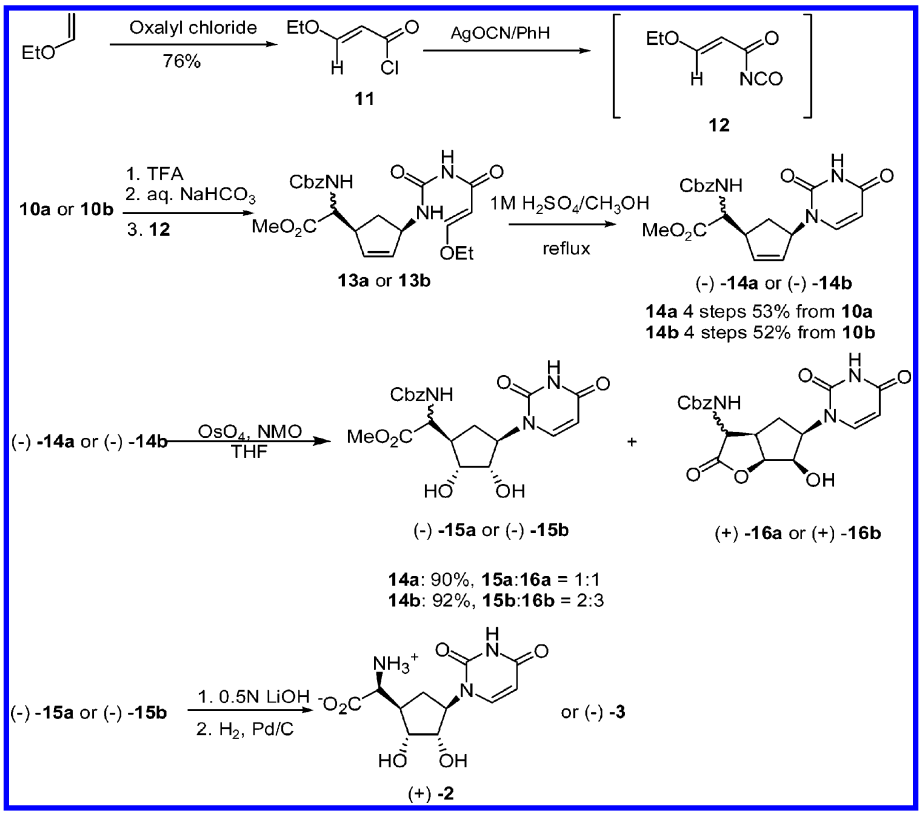
SCHEME 4



bonate in THF to provide **10a** and its α-epimer **10b** in a combined yield of more than 60% for three steps.

Next, the uracil base was incorporated using a modification of Shaw and Warrener's procedure.[15] Acid chloride **11** was prepared by reaction of vinyl ether and oxalyl chloride with subsequent decarbonylation in 76% yield after vacuum distillation.[16] The *N*-Boc group of **10a** or **10b** was removed by exposure to 50% TFA−CH_2Cl_2, and the crude TFA salt was washed with saturated aqueous $NaHCO_3$ solution and extracted by EtOAc. The crude amine then was treated with acyl isocyanate **12** which was obtained by refluxing **11** with AgOCN in benzene to give the intermediate methyl ester **13a** or **13b** in good yields. Esters **13a** and **13b** were refluxed in 1:1 1 N sulfuric acid solution and methanol to provide uridines **14a** and **14b**, respectively. Formation of the protected carbocyclic polyoxin C derivative **15** was accomplished by dihydroxylation of **14** with catalytic OsO_4 and NMO in THF. Under a variety of conditions,[17] the diols **15** and lactones **16** were obtained in an approximately 1:1 ratio. The undesired *syn*-diol spontaneously formed a lactone as previously reported,[12,18] thus simplifying purification of the desired diol. Final deprotection was then accomplished by hydrolysis of methyl esters (**15a** and **15b**) using 0.5 N LiOH aqueous solution in methanol, followed by removal of the benzyl groups by hydrogenolysis over 10% Pd/C to give carbocyclic uracil polyoxin C (+)-**2** and its α-epimer (−)-**3** (Scheme 4).

We have reported an asymmetric synthesis of carbocyclic uracil polyoxin C (+)-**2** and its α-epimer (−)-**3** in an efficient fashion. The synthesis highlighted a concise, inexpensive chemoenzymatic synthesis of enantiopure aminocyclopentenols, a Pd(0)-catalyzed substitution reaction and a mild reduction of an α-nitro ester by $TiCl_3$/sodium borohydride. These features would allow an efficient synthesis of all major carbocyclic polyoxin C analogues in an asymmetric fashion. Significantly, this synthetic exercise demonstrates new utility for the versatile enantiopure aminocyclopentenol-based building blocks.

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Supporting Information Available: Complete experimental details, compound characterization, and ^1H and ^{13}C NMR spectra for (+)-**2**, (−)-**3**, (+)-**16a**, (+)-**16b**, (−)-**15a**, (−)-**15b**, (−)-**14a**, (−) -**14b**, (−)-**10a**, (−)-**10b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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