Palladium-Catalyzed Substitution of Unsaturated Lactones. Application to the Synthesis of Carbocyclic Polyoxins and Nikkomycins

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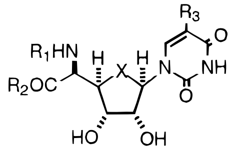
Carbocyclic analogues of nucleosides display a wide range of biological activity and have attracted particular attention as antitumor[1] and antiviral agents.[2] The potential advantage in the therapeutic use of these compounds include greater metabolic stability and in some cases *increased* biological activity compared to nucleosides. These features have fueled an explosion of interest in the design and synthesis of further analogues of this class of compounds.[3] However, little attention has been given to the carbocyclic analogues of the nikkomycins or polyoxins, a class of nucleosides in which the 5′ position is substituted by an amino acid.[4] The natural compounds exhibit selective activity against certain pathogenic fungi by preventing fungal cell wall growth through inhibition of the enzyme chitin synthase, but are nontoxic to bacteria, plants, and mammals.[5] As this enzyme is also found in insects, these compounds are also effective insecticides. In this paper we describe the first stereospecific total synthesis of the carbocyclic analogue **1** of uracil polyoxin C and significant findings related to palladium-catalyzed substitution reactions.

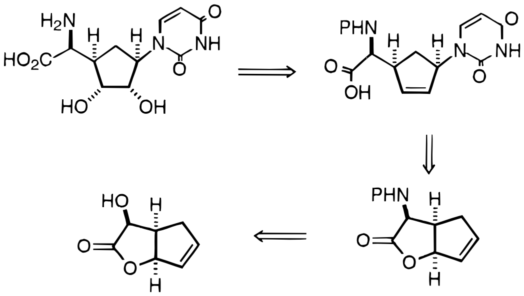


Nikkomycins and Polyoxins, X = O
R_1 = C-terminal amino acid
R_2 = N-terminal amino acid or OH
R_3 = H, CH_3, CH_2OH, CO_2H

Carbocyclic Uracil Polyoxin C
X = C ; R_1, R_3 = H; R_2 = OH **1**

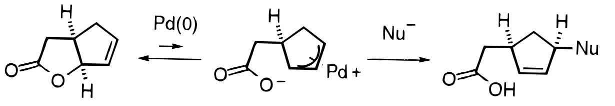
Our strategy toward this class of molecules involved a palladium-catalyzed substitution reaction of an unsaturated lactone as the key step as shown in Scheme 1. There appears to be only one example of an *unstrained* lactone being opened by a nucleophile under palladium catalysis, and this lack of precedence provided further impetus for us to explore this class of reactions.[6]

Scheme 1



Initial attempts at opening the model lactone **2** using Pd(0) with either uracil anion or the more nucleophilic NaN_3 met with failure.

Unlike the situation with allylic acetates or carbonates, with unsaturated lactones the intermediate π-allyl palladium species has an internal nucleophile, the carboxylate, which competes with the external nucleophile during the substitution step. There is, therefore, an equilibrium between the lactone and the intermediate π-allyl palladium species. With unstrained lactones this equilibrium is very much on the side of the lactone and



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only exceptionally good nucleophiles, like dimethyl malonate,[6] can react with the very small amount of the intermediate π-allyl palladium species present. With strained lactones the equilibrium is shifted toward the intermediate π-allyl palladium species, and they can now react with less reactive nucleophiles.[7] We therefore needed to influence the position of this equilibrium. We reasoned that an additional substituent α to the carbonyl group should achieve this as the *endo* isomer should shift the equilibrium toward the intermediate π-allyl palladium species relative to the *exo* isomer due to the additional strain introduced upon ring closure back to the lactone (Scheme 2). We initially prepared the two hydroxy lactones[8] **2a** and **3a** in racemic form and reacted them with sodium diethyl malonate, and we observed a dramatic difference in reactivity of the two isomers. The *endo* isomer **3a** gave a complete reaction after only 1 h at room temperature while the *exo* isomer **2a** gave essentially no product even after several days in refluxing THF. The previously reported unsubstituted lactone reacts at an intermediate rate.[6]

The two bromo lactones were also prepared[9] and reacted with sodium diethyl malonate, but this time both the *endo* and *exo* isomers reacted although the *endo* isomer **3b** reacted more quickly than the *exo* isomer **2b**. However, both reactions led to the *same* diastereomer **5b**. This indicated that the *exo* isomer **2b** epimerized slowly to give some of the *more strained endo* lactone **3b**, and this species then underwent palladium-catalyzed allylic substitution. The scope of the reaction was determined

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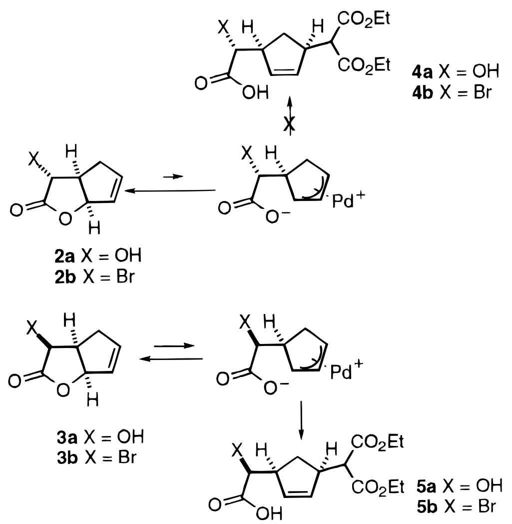
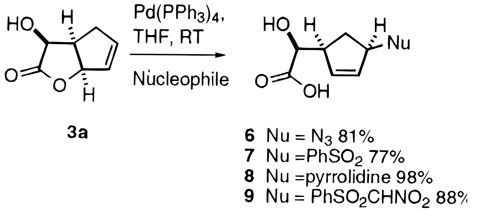
Scheme 2

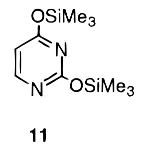


for the *endo* hydroxy lactone **3a** which was found to react with a broad range of nucleophiles (Scheme 3).

Scheme 3



Having solved the problem of lactone opening, we embarked on our synthesis of the carbocyclic analogue of the nikkomycins. Enantiomerically pure lactone (−)-**3a**[10] was converted to the amino compound **10** with overall retention of configuration. This was reacted with the anion of uracil in the presence of Pd(0) but no coupling occurred under a variety of conditions. While we were confident from our earlier studies that **10** could react with NaN_3 under palladium catalysis and that we could then build up the pyrimidine ring using standard procedures,[11] the additional steps and linearity of the synthesis would make it less efficient and less flexible. Nucleoside bases have successfully been used in Pd(0)-catalyzed coupling reactions with simple allylic acetates[12] but are known to be rather poor nucleophiles and evidently are not sufficiently potent to react even with *endo* substituted lactones. Assuming that the problem still lay in the position of the equilibrium favoring the closed lactone rather than the π-allyl palladium species, we sought to drive the reaction over by trapping the carboxylate released with TMSCl. We were pleased to find that treatment of **10** with *O*,*O*-bis(trimethylsilyl)-uracil[13] (**11**) in the presence of TMSCl gave clean coupling and following benzylation of the acid, **12** was isolated in 50% yield. In the absence of TMSCl no coupling occurred. The penultimate step in the synthesis was stereocontrolled dihydroxylation of the cyclopentene, and a variety of reaction conditions were examined. The highest yield was obtained using 4-methylmorpholine *N*-oxide (NMO)[14] with catalytic OsO_4 in THF (90%) but as a 1:1 mixture of **13**:**14**.[15] **14** resulted from lactonization of the undesired diol, and this transformation aided separation of the two isomeric products and confirmed the stereochemistry of the dihydroxylation. Finally, hydrogenolysis of



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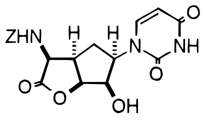

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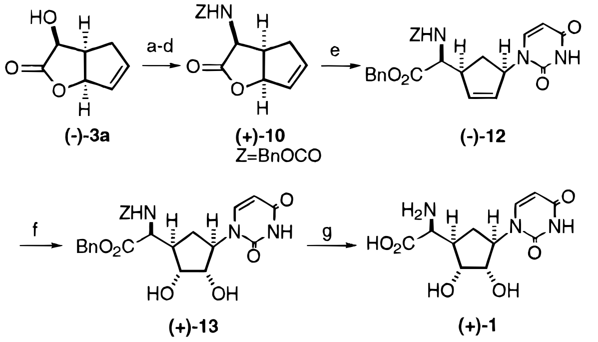
both benzyl protecting groups was achieved in essentially quantitative yield.



(a) $ZnBr_2$, PPh_3, DEAD, THF, RT, 60%. (b) NaN_3, DMSO, RT, 87% (c) PPh_3, THF-H_2O, RT, 92%. (d) ZCl, $NaHCO_3$, THF-H_2O, 0°C, 94%. (e) Uracil, $(Me_3Si)_2NH$, Me_3SiCl, cat $Pd(PPh_3)_4$, CH_3CN, RT; then BnBr, $NaHCO_3$, DMF, RT, 50%. (f) NMO, cat OsO_4, THF, RT, 44%. (g) H_2 (1 atm), Pd/C (10%), EtOH-H_2O, RT, 100%.

In summary, we have described a short, practical, asymmetric route to carbocyclic analogues of the nikkomycins and polyoxins. In addition, we have discovered the factors that are important for achieving palladium-catalyzed substitution reactions of unsaturated lactones, and as many of these compounds are now available in enantiomerically pure form this greatly expands their synthetic utility.

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Supporting Information Available: Syntheses and spectral data for **1**, **2b**, **3b**, **5a**,**b**, **6**−**10**, **12**, and **13** (6 pages).

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