A Transition-Metal-Controlled Synthesis of (±)-Aristeromycin and (±)-2′,3′-*diepi*-Aristeromycin. An Unusual Directive Effect in Hydroxylations

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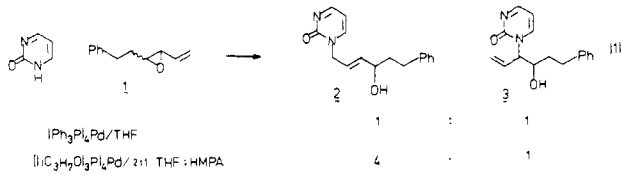
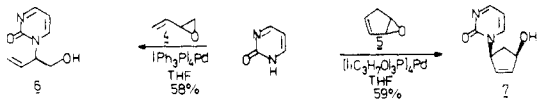
The biological significance of carbocyclic analogues of nucleosides and of hydroxyalkylated purines[1] and the widespread use of protecting groups in the synthesis of such compounds led us to explore whether transition-metal-catalyzed alkylations would enhance selectivity and, consequently, improve synthetic efficiency. An initial question relates to regioselectivity as exemplified by the reaction of 2-pyrimidinone with vinyl epoxide **1** (eq 1). Unlike

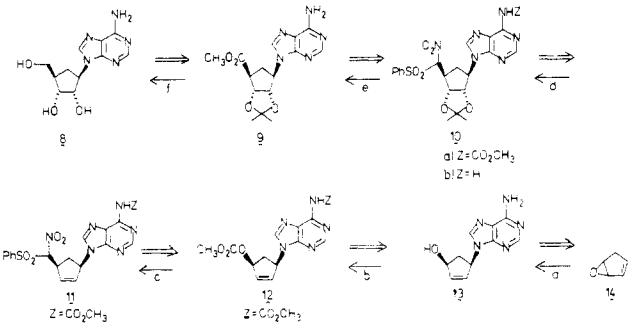


the case of carbon nucleophiles,[2] a lower propensity for attack distal to oxygen to give the 1,4-product exists.[3] The ratio of **2**:**3** increases by switching from THF to 2:1 THF/HMPA and also by using triisopropyl phosphite rather than triphenylphosphine as ligand. The choice of vinyl epoxide can also play a role as shown by the contrast between the acyclic and cyclic epoxides **4** and **5** in which exclusive 1,2-attack can be achieved in the former case to give **6**[4] and 1,4-attack in the latter case to give **7**.[4]



The success of the latter experiment led us to explore a synthesis of the carbanucleoside natural product aristeromycin[5,6] in which the regio- and diastereoselectivity of the 1,4-substitution would be totally controlled by Pd(0) templates. During the course of these studies, we discovered a most unusual directive effect in cis hydroxylations[7] which permits a stereocontrolled synthesis of both the natural product and its 2′,3′-diepi or lyxo isomer.

Scheme I.[a] Retrosynthetic Analysis and Synthesis of (±)-Aristeromycin



[a] (a) 0.6 mol % $Pd(OAc)_2$, 6 mol % $(i\text{-}C_3H_7O)_3P$, 1.2 mol % $n\text{-}C_4H_9Li$, 1 equiv of adenine, 1:1 THF/DMSO, 0 °C to room temperature, 67% (based upon recovered adenine). (b) $ClCO_2CH_3$, C_5H_5N, CH_2Cl_2, 0 °C to room temperature, 85%. (c) $LiCH(NO_2)SO_2Ph$, 5 mol % $(dba)_3Pd_2(CHCl_3)$, 50 mol % Ph_3P, THF, reflux, 82%. (d) i. $KMnO_4$, 0.6% aqueous NaOH, H_2O, 0 °C; ii. TsOH, $(CH_3)_2C(OCH_3)_2$, $(CH_3)_2CO$, 50 °C, 45%. (e) i. NH_4OH, CH_3OH, room temperature, 81%; ii. $NaOCH_3$, CH_3OH, O_3, −78 °C, 70%. (f) i. DIBAL-H, 1:1 CH_2Cl_2/PhH, 45 °C, 82%; ii. 1.5 M aqueous HCl, 80 °C then Dowex IX8-50 (OH form), 70%.

Scheme I outlines the retrosynthetic analysis and synthesis of aristeromycin (**8**). By equating the hydroxymethyl group of **8** with an ester as in **9** and consequently a nitrosulfone as in **10**, we make the critical correlation of the 2,3-cis hydroxyl substitution as deriving from a sterically least-hindered cis hydroxylation of an olefin as in **11**. The choice of nitrophenylsulfonylmethane as a carboxy equivalent derives from its ability to serve as a nucleophile in Pd(0)-mediated alkylations.[8] Thus, we have two substituents, each one of which can serve as a nucleophile, situated in a cis 1,4-fashion on a cyclopentene ring—an ideal orientation for Pd(0)-controlled reactions starting from cyclopentadiene monoepoxide.

Using 0.6 mol % of $[i\text{-}C_3H_7O)_3P]_4Pd$ generated in situ[9] with a 1:1 ratio of adenine and cyclopentadiene monoepoxide at 0 °C for 3 h and 25 °C for overnight gave the cis 1,4-alkylated product **13** whose structure is fully secured by its spectroscopic data.[4] Alkylation of N-9 of the adenine is consistent with other base-promoted reactions of adenine with saturated epoxides.[10] Substitution of the generated allylic alcohol must now occur with retention of configuration—a type of process that is nicely provided by Pd(0) templates[11] as shown in the transformation of the carbonate **12**[4] into the desired 1,4-cis-disubstituted cyclopentene **11**.[4,12]

Cis hydroxylation was anticipated to proceed on the sterically least-hindered face trans to both groups. Treatment with catalytic osmium tetroxide and a stoichiometric amount of *N*-methylmorpholine *N*-oxide[13] in aqueous THF followed immediately by conversion to the corresponding acetonide produced presumably **10a** and, after base hydrolysis, **10b**. The conversion of the nitrosulfone to a carboxylic acid equivalent required ozonolyzing[14] a methanolic sodium methoxide solution of the nitrosulfone to give the presumed ester **9** in 75% yield. DIBAL-H reduction of the

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(9) Generated by treating a mixture of palladium acetate and triisopropyl phosphite with *n*-butyllithium in THF (Pd:P:RLi, 1:10:2). In our own laboratories, this reaction was performed on a 32-mmol scale; substantial increase in scale is possible.

(10) Martin, J. C.; Smee, D. F.; Verheyden, J. P. H. *J. Org. Chem.* **1985**, *50*, 755.

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(12) Compounds **10**, **11**, **15**, **19**, and **21** are 1:1 diastereomeric mixtures at the carbon bearing the sulfone and nitro groups.

(13) Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.

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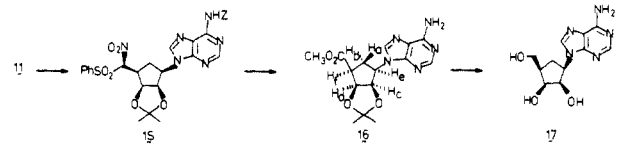
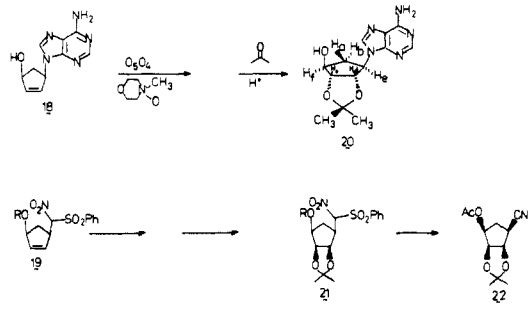
ester to the alcohol (83% yield) and aqueous hydrochloric acid hydrolysis followed by neutralization with a basic resin gave a single carbanucleoside in 66% yield. Neither the mp of the synthetic product (mp 168–70 °C) nor the spectral data (^1H and ^{13}C NMR) corresponded to (±)-aristeromycin.

Since the spectral data for both **13** and **11** appeared totally in agreement with the assigned structures, we considered whether the cis hydroxylation may have been "directed" to the more hindered face to give **15**.[4] A NOE study of the corresponding



methyl ester **16**[4] showed irradiation of H_b enhanced both H_e (8.3%) and H_f (5.6%) in agreement with the cis 1,4-relationship of the ester and the adenine. Irradiation of H_c enhanced both H_d and H_e indicating their cis relationship, and irradiation of H_d enhanced both H_c and H_f indicating their cis relationship. Thus, all of the structures starting from the cis hydroxylation product to the end must be reassigned as **15–17**,[4] and the final product, then, is (±)-*lyxo*-aristeromycin (**17**).[4]

To probe the source of the unusual hydroxylation stereochemistry, we hydroxylated **18** and **19**. NMR Eu(+3) induced shift studies allow assignment of the stereochemistry of **20**[4] as trans as "expected".[15] An NOE study of the nitrile **22**, derived from



the initial hydroxylation product **21** upon treatment with titanium trichloride,[8] showed the same pattern as for **16**—confirming the "abnormal" all cis orientation. Comparison of the results of the reaction of **11**, **18**, and **19** strongly implicates the nitrosulfonylmethane substituent as the director of the osmylation. Since sulfones are known not to direct osmylation,[7] it appears the source of the stereocontrol is coordination of osmium with the nitro group.

To resolve the issue of aristeromycin synthesis, we required a hydroxylation reagent that would not coordinate to the substituents present in **11**. Indeed, basic potassium permanganate[16] effects cis hydroxylation of **11** to give a product isomeric with **15**. This time, following the same sequence as before (use Scheme I), gave (±)-aristeromycin, whose spectral data is identical in all respects with an authentic sample.

The Pd-based reactions provide a very short and convenient synthesis of this carbacyclic nucleoside analogue. Other members may be readily created by similar means or through some of the intermediates reported herein. For example, introduction of a double bond in conjugation with the ester of **9** by sulfenylation–dehydrosulfenylation or the selenium equivalent followed by reduction forms neplanocin.[17] Furthermore, both the natural and the 2,3-di-epi series are available with complete stereocontrol. The unusual directive effect of the nitro group in cis hydroxylations via catalytic osmylations should prove valuable in stereocontrolled syntheses.

(15) Whereas H_a, H_c, and H_f shift by δ 1.13, 1.15, and 0.80 ppm upon adding 14.5 mol % $Eu(hfc)_3$, H_b and the two methyl groups only shift by δ 0.53, 0.17, and 0.16 under these conditions.

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Registry No. 4, 930-22-3; **5**, 54460-11-6; **6**, 111189-89-0; **7**, 111189-90-3; **8**, 13190-75-5; **9**, 111189-96-9; **10a** (diastereomer-1), 111189-94-7; **10a** (diastereomer-2), 111265-80-6; **10b** (diastereomer-1), 111189-95-8; **10b** (diastereomer-2), 111265-81-7; **11** (diastereomer-1), 111189-93-6; **11** (diastereomer-2), 111265-79-3; **12**, 111189-92-5; **13**, 111189-91-4; **15** (diastereomer-1), 111265-82-8; **15** (diastereomer-2), 111265-83-9; **16**, 111265-84-0; **17**, 72346-00-0; **20**, 111189-97-0; **22**, 111189-98-1; LiCH(NO$_2$)SO$_2$Ph, 74738-03-7; 2-pyrimidinone, 557-01-7; adenine, 73-24-5.

Supplementary Material Available: Spectral data for **6**, **7**, **8**, **9**, **11**, **13**, **16**, and **17** (2 pages). Ordering information is given on any current masthead page.

Hydrolysis Mechanisms of Alkynyl Benzoates, Tosylates, and Phosphates

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Alkynyl benzoates, tosylates, and phosphates have recently been prepared,[1a,b] and for RC≡COTs addition of protic acids HX shown to form RCH=CXOTs,[1c] while CH_3OH/K_2CO_3 gives $RCH_2CO_2CH_3$ and CH_3OTs.[1a] These compounds are of great interest for comparison to other ester types[2] and for the study of substitution of alkynyl systems,[3] and we now report that these substrates hydrolyze by several interesting mechanisms, including both electrophilic and nucleophilic attack on the triple bond.

In aqueous H_2SO_4 1-propynyl benzoate (**1**), diethyl 1-hexynyl phosphate (**2**), and 1-hexynyl tosylate (**3**) were found by ^1H NMR analysis of the reaction products to give the carboxylic acid corresponding to the alkynyl moiety, together with the acid derived from the acyl portion of each ester (eq 1–3). The reaction

$$CH_3C{\equiv}COBz\ (\mathbf{1}) \xrightarrow[H_2SO_4]{H_2O} CH_3CH_2CO_2H + BzOH \quad (1)$$

$$n\text{-}BuC{\equiv}COPO_3Et_2\ (\mathbf{2}) \xrightarrow[H_2SO_4]{H_2O} n\text{-}C_5H_{11}CO_2H + (EtO)_2PO_2H \quad (2)$$

$$n\text{-}BuC{\equiv}COTs\ (\mathbf{3}) \xrightarrow[H_2SO_4]{H_2O} n\text{-}C_5H_{11}CO_2H + TsOH \quad (3)$$

products from neutral aqueous solution containing CH_3CN cosolvent were reacted with CH_2N_2, and the methyl esters of the same acids were isolated and identified. The additional product

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