From Furan to Nucleosides

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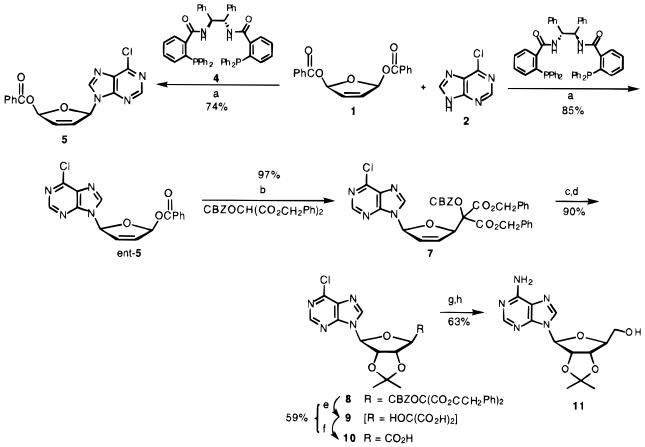
The potential therapeutic applications of nucleosides provide an ever increasing need for simple synthetic entries to them.[1,2] Almost without exception, their synthesis involves starting from a carbohydrate precursor for the furanose ring which raises the issue of chemoselectivity as well as diastereoselectivity of glycosylation. For some applications, significant deoxygenation may be required. A potentially useful new paradigm begins with *cis*-2,5-diacyloxy-2,5-dihydrofuran[3] which possesses displaceable substituents in the 2,5-positions with the correct stereochemistry for entry into the nucleoside family using palladium catalysis. While elimination leading to aromatization is one obvious concern, the major issue to be resolved is asymmetric induction. Our recent successes in desymmetrization of carbocycles,[4] which has led to an asymmetric synthesis of carbanucleosides, led us to examine whether heterocycles also could be efficiently desymmetrized which may lead to an asymmetric nucleoside synthesis from *cis*-diester **1**, available in 76% yield as a crystalline solid, mp 174−5 °C, by the oxidation of furan with lead tetrabenzoate.[3]

While alkylation of these diacyloxydihydrofurans with 6-chloropurine (**2**) using achiral 1,2-diphenylphosphinoethane (dppe) as a ligand and $(dba)_3Pd_2{\cdot}CHCl_3$ (**3**, dba = dibenzylideneacetone) is not productive, the chiral **4** with the same Pd(0) source effects smooth alkylation as shown in Scheme 1 to give **5**[5] whose ee is established to be 93% by mandelate analysis of the *cis*-dihydroxylated product.[6] Recrystallization of **5** from ethyl acetate−hexane gives enantiomerically pure **5**,[5] mp 132−3 °C, $[\alpha]_D$ −135.6° (c = 2.6, CH_2Cl_2).

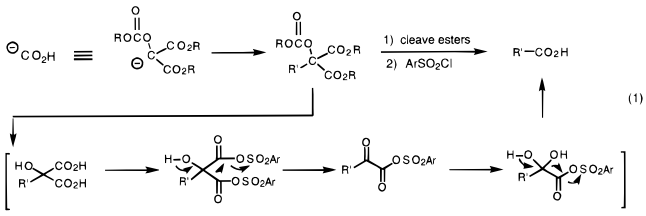
The advantage of this methodology is the simplicity of access to either enantiomer. Thus, the L-nucleosides[7] may be accessed simply by performing the reaction with the enantiomeric ligand ent-**5** as shown in Scheme 1 to give ent-**5**, mp 132−3 °C, $[\alpha]_D$ +136.0° (c = 2.6, CH_2Cl_2). To introduce the C-5 carbon, we

Scheme 1.[a] Alkylation with a Purine Base: a Synthesis of ent-Adenosine Acetonide



[a] (a) 1.1:1 ratio of **1**:**2**, $(C_2H_5)_3N$, THF, 2% **3**, 6% **4** or *ent*-**4**, rt. (b) 1.7% **3**, 12% Ph_3P, Cs_2CO_3, 1:1 THF:CH_3CN, rt. (c) 4% OsO_4, NMO, CH_2Cl_2, H_2O, rt. (d) $(CH_3)_2C(OCH_3)_2$, CH_3COCH_3, PPTS, CH_2Cl_2, 35 °C. (e) 1 atm H_2, 5% $Pd/BaSO_4$, 1:1 C_2H_5OAc:CH_3OH, rt. (f) $(C_2H_5)_3N$, *o*-$O_2NC_6H_4SO_2Cl$, CH_2Cl_2, −78 °C then moist C_2H_5OAc, rt. (g) HOBT, DCC, THF, rt then −10 °C, $NaBH_4$. (h) NH_4OH, CH_3CN, H_2O, rt.

initially investigated our use of (phenylsulfonyl)nitromethanes[8] in a second Pd(0)-catalyzed reaction unsuccessfully. We attributed the failure to the presence of an acidic hydrogen in the initial alkylation product that triggered decomposition. Thus, we devised a new $^-CO_2H$ equivalent as illustrated in eq 1 and



(1)

explored its use in a synthesis of ent-adenosine and an ent-NECA[9] intermediate as illustrated in Scheme 1. Dibenzyl benzyloxycarboxymalonate (**6**) participates extremely well in the second Pd(0)-catalyzed substitution with complete regio- and diastereoselectively to give **7**[5] virtually quantitatively. Dihydroxylation to give **8**[5] after acetonide formation is completely diastereoselective and *anti* as suggested by the ^1H NMR coupling constants ($J_{1,2}$ = 2.2 Hz and $J_{3,4}$ = 1.7 Hz) and proved by correlation to a known compound (*vide infra*). Catalytic hydrogenolysis generates the hydroxy diacid **9** which is directly subjected to *o*-nitrobenzenesulfonyl chloride and triethylamine. At −78 °C, the bis mixed anhydride forms and, upon warming to room temperature, decarbonylates to the α-keto mixed anhydride. At this point, ethyl acetate saturated with water is added to effect hydration and subsequent second decarbonylation to the desired acid **10**. Comparison of the spectral properties of the obtained acid **10** to those recorded for the D-isomer[10] shows their identity except for absolute configuration. Such carboxylic acids are frequently of interest. For example, the *N*-ethylcarboxamide in the D-series has proven to be one of the most interesting metabolically stable analogs of adenosine.[10] This new route provides either enantiomer of this series.

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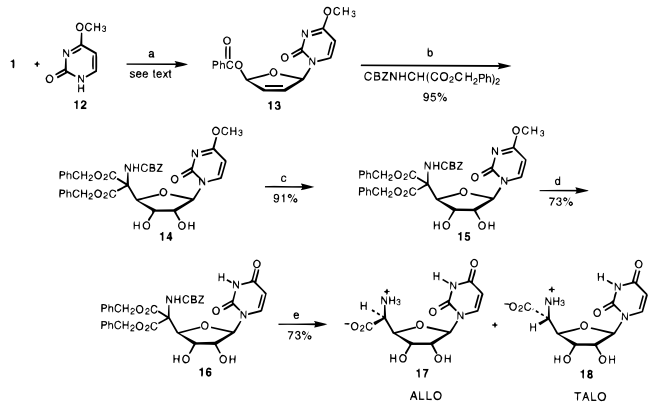
Scheme 2.[b] Synthesis of the Polyoxin−Nikkomycin Nucleoside Core



[a] (a) 1.25:1 ratio of **12**:**1**, 2% **3**, 7% **4**, $(C_2H_5)_3N{\cdot}HCl$, $(C_2H_5)_3N$, THF, 0 °C. (b) 2% **3**, 10% Ph_3P, Cs_2CO_3, CH_3CN, rt. (c) 6% OsO_4, NMO, $PhCH_3$:H_2O:CH_2Cl_2 (1:1.7:50), rt. (d) CF_3CO_2H, 1:9 H_2O:THF, reflux. (e) (i) H_2 (1 atm), $(C_2H_5)_3N$, 5% Pd/$BaSO_4$, CH_3OH, rt; (ii) $(C_2H_5)_3NH$ SO_3R (R = camphor), DMF:dioxane, rt.

Chemoselective reduction of the acid followed by aminoloysis generates the acetonide of ent-adenosine **11**[5,9,11] whose hydrolysis to ent-adenosine is well documented in the D-series.[12]

Use of a uracil equivalent as the nucleophile in the enantiodiscriminating step proved to be extraordinarily sensitive to the choice of heterocycle and the reaction conditions. Focusing on 4-methoxypyrimidin-2-one (**12**)[13] as the pronucleophile, the best conditions involve chloroform containing a 1:5 ratio of triethylamine hydrochloride to triethylamine at 0 °C to room temperature with 2% of palladium catalyst **3** and 7% of ligand **4** to produce **13**,[5] mp 182−3 °C, $[\alpha]_D$ −103.9° (c = 2.4, CH_2Cl_2) (65% yield, 85% yield brsm[14]), whose ee is determined to be >98% by the mandelate analysis of the *cis*-dihydroxylated product.[6] Availability of enantiomerically pure **13** provides a simple entry into the basic nucleoside skeleton of the polyoxin−nikkomycin complexes[15,16] as shown in Scheme 2. The allo (**17**,[16a] mp 237−240 °C, $[\alpha]_D$ +17.4° (c = 0.50, H_2O)) and talo (**18**,[16a] mp 214−7 °C, $[\alpha]_D$ +9.6° (c = 0.5, H_2O)) isomers, whose structures are confirmed by comparison to authentic samples,[16a] are obtained in nearly equal amounts.

The ability to effect Pd(0)-catalyzed alkylations without eliminations to the aromatic furans with 2,5-diacyloxy-2,5-dihydrofurans[17] and the advantage of chiral vs achiral ligands in just effecting such alkylations are noteworthy. Sequential Pd(0)-catalyzed reactions first with chiral then with achiral ligands provide in three steps from furan appropriately alkylated and enantiomerically pure *cis*-2,5-disubstituted-2,5-dihydrofurans suitable for further elaboration to nucleoside analogues. The prospect of performing the two Pd(0)-catalyzed steps in a single pot may further simplify the synthesis. Furthermore, the nature of either the 2- or 5-substituent can be readily varied by choice of nucleophiles as illustrated by the two applications outlined. This route provides the dihydrofurans initially: a highly desireable feature since (1) they are frequently the desired target and therefore their cumbersome syntheses from sugars may be avoided and (2) the absence of extra hydroxyl groups as in the case of the normal strategies from sugars diminishes chemoselectivity problems. Thus, 2,3-dideoxy, 2- or 3-deoxy, and the normal nucleosides and their analogues should be readily available by this methodology. It also provides the uronic acids directly, thereby circumventing the frequently troublesome oxidation of C-5.[11,18] The effectiveness of this chemistry is illustrated by the availability of L-nucleosides in nine steps from furan in 18% overall yield and of the polyoxin−nikkomycin core in only six steps and 39% overall yield. The development of acyloxymalonates as a hydroxycarbonyl anion equivalent in Pd(0) reactions also should prove generally useful for stereospecific introduction of this versatile functional group.

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Supporting Information Available: Characterization data for compounds **5**, **7**, **8**, **10**, **11**, and **13**−**16** (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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