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Synthesis of D-D4FC, a biologically active nucleoside via an unprecedented palladium mediated Ferrier rearrangement-type glycosidation with an aromatization prone xylo-furanoid glycal

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Abstract—D-D4FC (**1**) is an anti-HIV agent currently under phase II clinical trial (Pharmaset Inc). Its molecular architecture is suitable for a Ferrier rearrangement kind of operation on a furanoid glycal to fix the position of the double bond and the relative stereochemistry. Despite the fact that classical Ferrier rearrangement does not work on furanoid glycals, a palladium mediated modified protocol has been developed for the glycosidation of an aromatization prone xylo-furanoid glycal (**5**) for the synthesis of D-D4FC.

The Ferrier rearrangement of glycals is a well-known synthetic method in sugar chemistry.[1] Generally, a six membered ring 1,2-glycal bearing a leaving group adjacent to the double bond undergoes an acid catalyzed formation of an oxocarbonium ion that traps a nucleophile to form a glycosidic bond (Chart 1).[2] On the other hand, though the five membered 1,2-glycals are more prone to Ferrier rearrangement on stereoelectronic grounds,[3] there is no synthetically useful example in the literature utilizing this reaction to best of our knowledge. The reason could be the Ferrier rearrangement itself, as it causes inherent instability of furanoid glycal bearing a leaving group at 3-position due to protic solvents or H_2O acting as nucleophiles, thus resulting the isolation of glycal

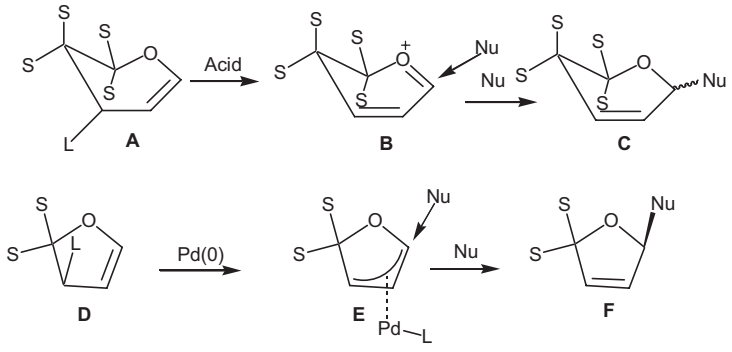

Chart 1.

Keywords: Nucleoside; D-D4FC; Glycosylation; Furanoid glycal; π-Allyl palladium.
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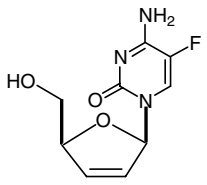
difficult.[4] Moreover, glycosidation by Ferrier rearrangement requires acidic reaction conditions,[5] under which furanoid glycals undergo aromatization.[6] The stereoselectivity of such reactions in general are also unpredictable though the anomeric effect in some cases dictates the stereochemical out come. In a plan to utilize such an allylic rearrangement in nucleoside formation, we envisioned that generating the sensitive glycal in situ, and re-directing the course of the reaction by Pd(0), in place of a strong Lewis acid, would allow the formation of a π-allyl intermediate that would block one face of the glycal (**E**, Chart 1). It would direct the incoming nucleophile from an opposite face and also in a regio-selective fashion at the more electrophilic anomeric carbon (**F**, Chart 1). As a result, this would establish the β-glycosidic bond stereospecifically along with the double bond in 2-, 3-position. This paper describes the successful implementation of such concept for a short and concise synthesis of 2′,3′-didehydro-2,3-dideoxy-5-fluorocytidine (D-D4FC, **1**),[7] a reverse transcriptase inhibitor starting from an aromatization prone xylo-furanoid glycal and an *unprotected* fluoro cytosine as the nucleophile. We have also demonstrated the successful isolation of the reportedly unstable glycal (**5**, Scheme 1) for the first time.



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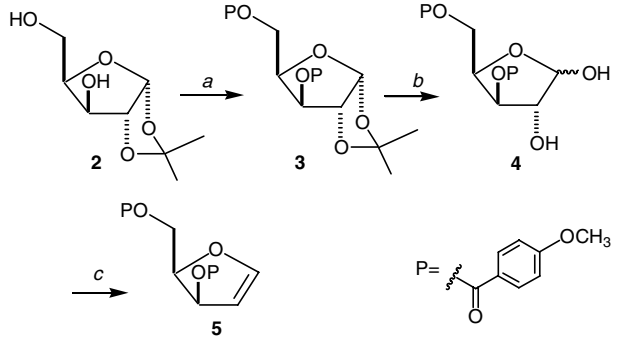
Our first task was to address the stability of the requisite precursor glycal **5**. The isolation of these kinds of glycals are difficult due to their inherent instability.[4,6,8] Ireland and co-workers have reasoned that the incipient instability of these species is due to the near coplanarity of the enol–ether double bond and the C3–oxygen bond of the glycal.[3] By attenuating the nature of departing group or by specially designed protocols, it has been possible to isolate ribofuranoid glycals.[4,9] However, isolation of a xylofuranoid glycal with a proximal leaving group has never been demonstrated, although the existence of such species in solution have been implicated by ^{1}H NMR[10] and they have been used via in situ generation.[11]



Scheme 1. Reagents and conditions: (a) *p*-anisoyl chloride, Py, rt–50 °C, 95%; (b) AcOH/H_2O (1:2), 97 °C, 5h, 86%; (c) I_2, Pol-TPP/imidazole, 33%.

For successful generation of π-allyl intermediate **E** (Chart 1) that would block the α face, it was required to synthesize the glycal (**5**) of xylofuranose stereochemistry. We planned to generate the glycal in situ by adopting a similar route described for the synthesis of 1,4-anhydro-3′,5′-di-*p*-methoxybenzoyloxy-2-deoxy-D-threo-pent-1-enitol, one of the very few successful methods reported.[12]

Our synthesis commences with commercially available 1,2-isopropylidine D-(+)-xylofuranose (**2**), which is easily prepared from (D)-(+)-xylose, an inexpensive pyranose sugar. Introduction of a leaving group and a suitable protecting group at 3′,5′-hydroxy groups, respectively, was done using *p*-anisoyl chloride in pyridine to afford **3**.[13] Deketalization of the acetonide resulted anomeric mixture of diols (**4**). Subsequent conversion of the crude diols (>96% pure) to the 1,2-glycal (**5**) was accomplished by using I_2/Ph_3P/imidazole (Scheme 1). This reaction seems to proceed via the elimination of 1,2-di-iodo compound. The *trans*-1,2-di-iodo compound undergoes facile elimination compared to the corresponding *cis* compound. However, triphenyl phosphine oxide (TPPO), the by-product of this reaction was difficult to remove completely from the reaction mixture. The glycal was found to be unstable to chromatography and use of this crude glycal in the Pd mediated coupling reaction resulted in the desired product **1** in lower yield. Employment of resin bound Ph_3P, however, solved the problem, as the by-product (TPPO) could be removed by simple filtration during the reaction work-up. Thus, by using resinbound Ph_3P, the glycal (**5**) purity was enhanced to more than 90% and this product could be isolated for the first time.[14]

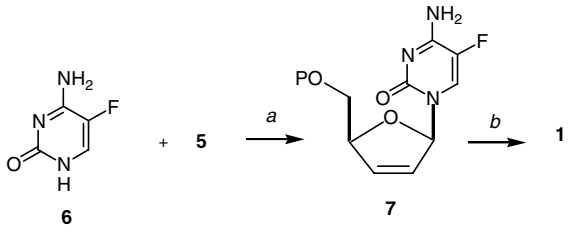
The next challenge was to address the key glycosylation process. Literature shows that metal mediated coupling reactions have been successfully used for bond formation at the anomeric center of a sugar to make O- and *N*-glycoside,[15] furanoid *C*-glycosides[16] and pyranoid *C*-glycosides.[17] Trost and co-workers have used a non-sugar, palladium based approach to form nucleosides via asymmetric desymmetrization of *cis*-diacyloxy-dihydrofuran.[18] However, metal-coupling reactions involving nitrogen nucleophiles bearing additional nitrogen or other heteroatoms is not straightforward,[19] often requiring protection to ensure a smooth bond forming process. The glycosylation reaction was optimized (Table 1) with respect to base using acetonitrile as the solvent and 10 mol % $Pd(Ph_3P)_4$ at 30 °C for 24 h using an unprotected nucleoside base **6**. In a blank run, the reaction seems to proceed without base but was very slow. Observation of significant amount of aromatized glycal necessitated the use of a base.

After some optimization (Table 1) it was found DBU and NMP to be suitable base and solvent, respectively. Use of 3 mol % $Pd(Ph_3P)_4$ was found to be optimal. As shown in Table 1, pempidine was found to give the

Table 1. Effect of base

Base	% Conversion[a]	Base	% Conversion[a]
Pempidine	65–70	TBA	50
DIPEA	25	DBU	60
NaH	50	TEA	25–30

[a] Reactions stops after the conversion shown, remainder of the glycal aromatizes.



Scheme 2. Reagents and conditions: (a) DBU, NMP, 3 mol % Pd(0), 33 °C, 2 d, 76–80% conversion, 50% isolated yield; (b) 7 mol % NaOMe/MeOH, 18 h, 82%.

highest conversion and cleaner reaction profile. But for high cost of pempidine, we preferred to use DBU as the base of choice. Catalyst loading was optimized with DBU as the base and acetonitrile as the solvent. Among the variations tried, that is, 1%, 3%, 10%, 3 mol % was found to be the optimal. Optimization of the solvent (NMP, DMF, toluene, DCM, acetonitrile) with DBU as the base with 3 mol % of $Pd(Ph_3P)_4$ as the catalyst showed NMP as the solvent of choice.

A Ferrier type allylic coupling of the unprotected base, fluorocytocine (**6**) with glycal **5** in the presence of $Pd(Ph_3P)_4$ (tetrakis-triphenyl phosphine palladium(0)) catalyst[20] provided the 5′-anisoyl-DD4FC in good isolated yield (Scheme 2).

It is worth noting that sequence of addition of reagents is critical for success of these reactions.[20,21] The isolation of the nucleoside was extremely simple and required no chromatography. The reaction mixture was poured into water and the mixture was extracted with ethylacetate. Solvent exchange with toluene generated **7**, which on subsequent deprotection of 5′-anisoyl group provided the DD4FC. The product (**1**) has identical HPLC retention times, ^{19}F, ^{1}H, and ^{13}C NMR spectrum with authentic DD4FC (**13**).[22]

In conclusion, we have demonstrated that the aromatization prone glycal can be successfully used in a Ferrier rearrangement type products generation using Pd(0) as the catalyst. The high regio and stereoselective product formation leads to a concise synthesis of DD4FC, a nucleoside reverse transcriptase inhibitor. We have also demonstrated that this coupling reaction can be extended to other nucleophiles.

Acknowledgement

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14. No aromatized product was observed. The rest of the impurity seemed to come from the resin. It was found that 10 upon concentration using 2:1 hexanes/toluene becomes a solid but generate more impurity. The preferred way to save it is as a solution in acetonitrile stored over 4 Å molecular sieves free of moisture and acids. This way of preservation retains the stability of the glycal at least over 2–3 weeks without degradation.
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20. Control experiment via fluorine and proton NMR in tetrahydrofuran-*d*8 showed that the glycal 10 aromatizes to furan derivative (50% in 0.5 h) in presence of tetrakis triphenyl phosphine Palladium(0) and in the absence of an added nucleophile.
21. Addition of catalyst to the glycal at room temperature causes aromatization, but when catalyst is added to a

pre-mixture of solvent, fluorocytosine, DBU, and glycal smooth product formation was noticed.

22. *Synthesis of 1,2-O-isopropylidene-3,5-di-O-p-methoxybenzoyl-*D*-xylofuranose* (**3**): To a solution of 1,2-*O*-isopropylidene-D-xylofuranose (190.2 g, 1 mol) in anhydrous pyridine (254 mL) was added *p*-methoxybenzoyl chloride slowly, keeping temperature below 50 °C. At the end of the addition the thick slurry was heated at 60–65 °C for 6.5 h. The reaction mixture then cool to 34 °C and a total volume of 350 mL of water was added. The mixture was stirred at 40 °C, slowly cooled down to a slurry, and was filtered at 30 °C. The solids product was washed with water/MeOH 9/1, vacuum dried at 45–50 °C to give 437.6 g (95.4% yield) of the desired product. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.97 (d, $J = 8.7$ Hz, 4H), 6.9 (t, $J = 8.7$ Hz 4H), 6.05 (d, $J = 3.7$ Hz, 1H), 5.56 (d, $J = 2.9$ Hz), 4.76 (m, 1H), 4.6 (m, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 1.57 (s, 3H), 1.34 (s, 3H). ^{13}C NMR ($CDCl_3$): 156.9, 164.9, 163.9, 163.5, 131.9, 131.9, 121.9, 121.3, 113.8, 113.6, 112.4, 105.1, 83.5, 76.7, 76.4, 61.7, 55.5, 55.4, 26.75, 26.2.
*Synthesis of 3,5-di-O-p-methoxybenzoyl-*D*-xylofuranose* (**4**): To a slurry of 1,2-*O*-isopropylidene-3,5-di-*O*-*p*-methoxybenzoyl-D-xylofuranose (92 g, 0.2 mol) in acetic acid and water (184 and 368 mL) was added 2.3 g (22.2 mmol) of concd H_2SO_4. The slurry was heated and became a clear solution after about 1 h at 90–95 °C. After 5 h at 95 °C there was no trace of the starting acetonide. The reaction mixture was cooled to room temperature and the solvents were evaporatively removed to a minimum. The oily residue was dissolved in 300 mL of CH_2Cl_2 and 200 mL of water, and neutralized to pH 7–8 with aqueous $NaHCO_3$ and NaOH solutions. The organic phase was dried over $MgSO_4$, the solvent evaporated and the residue was vacuum dried at room temperature to give a 96.3 g of the crude product 3,5-di-*O*-*p*-methoxybenzoyl-D-xylofuranose apparently still wet with solvent. The crude product was redissolved in CH_2Cl_2 and kept as stock solution. Estimated yield is 70% with about 90% purity.
*1,4-anhydro-3′,5′-di-p-methoxybenzoyloxy-2-deoxy-*D*-threo-pent-1-enitol* (**5**): To a 4n-2 L reactor with N_2-adaptor, mechanical stirrer, and thermocouple CH_2Cl_2 (250 mL) was added and stirred. Iodine (17.26 g, 68 mmol) was added and stirred unti dissolution. Polymer bound triphenylphosphine (22.67 g, 68 mmol) was charged all at a time and stirred. The flask was allowed to naturally cool to ambient temperature. At ambient temperature imidazole (9.25 g, 136 mmol) was added and stirred for 15 min. Then 100 mL of 4 (34 mmol as solution in dichloromethane) was added all at a time. The resultant heterogeneous mixture was stirred for 1 h at ambient temperature. The solids were filtered off by a dacron, washed thoroughly with 100 mL of dichloromethane Treat the stirring filtrate by slow addition of a mixture of 75 mL satd $Na_2S_2O_3$ + 50 mL of satd $NaHCO_3$. Separate the bottom organic layer. pH of the top aqueous, 129 mL, pH = 9. Wash with organics with 500 mL H_2O. pH = 9 (aqueous). Final brine wash 100 mL. Organics were separated and concentrated to an oil. Yield = 23% ^{1}H NMR ($CDCl_3$, 300 MHz): 7.91 (2H, d, $J = 9.1$), 7.85 (2H, d, $J = 8.9$), 6.08 (1H, ddd, $J = 2.7$, 0.9, 2 Hz), 5.29 (1H, m), 4.78–4.60 (3H, 2m), 3.79 (s, 3H), 3.78 (s, 3H). 4-Methoxy-benzoic acid 5-(4-amino-5-fluoro-2-oxo-2H-pyrimidin-1-yl)-2,5-dihydro-furan-2-ylmethyl ester (**7**): To a 50 mL 1-neck reactor with a magnetic stirrer was charged Fluorocytocin (387 mg, 3 mmol) followed by 5 mL of NMP. DBU (450 μL, 3 mmol) was charged to the reactor. To the stirring mixture was added glycal (1.15 g) in 10 mL of NMP. The reaction mass was evacuated and filled with argon three times. $Pd(Ph_3P)_4$ (108 mg, 0.093 mmol, 3 mol %) was added to the stirring mass. The reaction mass was degassed and filled with argon. Acetonitrile (0.4 mL) was added to the reactor. The reaction mass was warmed to 33 °C and stirred for 48 h. The conversion was monitored by ^{19}F NMR and was shown to be 76% complete. It was cooled to room temperature. The reaction mass was partitioned between water (50 mL) and ethyl acetate (70 mL). Brine (20 mL) was added to break the emulsion and the mixture was shaken vigorously. The aqueous layer was separated and extracted once more with ethylacetate (50 mL). The combined organics were again washed with 50 mL of 50% aqueous NaCl. The organics were dried over anhydrous Na_2SO_4, filtered to a brown oil. The oil was suspended in 10 mL of toluene and stirred overnight. The precipitated solids were filtered off. The reactor and filtered solids were washed with 10 mL of toluene to provide pure 5′-anisoyl DD_4FC as pure solid after drying (373 mg, 35%). 19 F NMR: m, −152.78 to 169.46 ppm.
2′,3′-Didehydro-2,3-dideoxy-5-fluorocytidine (*D-D4FC*, **1**): To a dry (oven dried, flushed with nitrogen) one neck 15 mL reactor with a stirring bar 5′-anisoyl D-D4FC (**5**, 100 mg, 0.277 mmol) was charged. Anhydrous MeOH (0.7 mL) was charged to the reactor followed by NaOMe/MeOH (0.5 M solution, 0.013 mmol, 5 mol %). The slurry was stirred for 19 h. It became a clear solution. The reaction mass was evaporated in vacuum to a solid. MeOH (0.5 mL) was added to it. The product precipitated out, which was filtered off. The filtered solids were washed with 0.5 mL of fresh MeOH. The product was dried in vacuum oven to provide 57 mg (82%) of the white crystalline solid. This material was identical to authentic D-D_4FC with respect to ^{1}H, ^{19}F,^{13} C, and HPLC retention time.