Organocatalysis

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Scalable Synthesis of the Potent HIV Inhibitor BMS-986001 by Non-Enzymatic Dynamic Kinetic Asymmetric Transformation (DYKAT)**

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Abstract: *Described herein is the synthesis of BMS-986001 by employing two novel organocatalytic transformations: 1) a highly selective pyranose to furanose ring tautomerization to access an advanced intermediate, and 2) an unprecedented small-molecule-mediated dynamic kinetic resolution to access a variety of enantiopure pyranones, one of which served as a versatile building block for the multigram, stereoselective, and chromatography-free synthesis of BMS-986001. The synthesis required five chemical transformations and resulted in a 44% overall yield.*

Since the FDA approval of azidothymidine (AZT) in 1987 as the first NRTI (nucleoside reverse transcriptase inhibitor) treatment of the HIV virus, the scientific community has been continuously searching for safer and more efficacious therapies. The last 20 years of research in this area has resulted in vastly improved therapeutics and treatment strategies.[1] Despite these improvements, viral drug resistance[2] and side-effects to the prescribed therapies remain outstanding issues.[3] BMS-986001 (**1**) is a thymidine NRTI which has been developed to maintain the in vivo antiviral activity demonstrated by other NRTI's, but lacks the associated toxicity side effects. Recent clinical data has shown this investigational therapy to be effective in reducing viral load while exhibiting a significantly improved safety profile, when compared to the standard of care.[4] To aid the development of this compound, a unique, expedient, and scalable synthesis of **1** was required. The development of this new route resulted in several interesting observations, and the development of two organocatalytic transformations to set key structural and stereochemical elements as described herein.

Retrosynthetic analysis of the targeted structure **1** led us to define pyranone (*S*)-**3** as the key enantioenriched building block from which a substrate-controlled, diastereoselective synthesis was envisioned (Figure 1). In the forward sense, a diastereoselective 1,4 addition of an arylthiol and subsequent 1,2-addition of the alkyne moiety would provide the pyranose **6b**. Next, a ring tautomerization/acylation sequence and a subsequent Vorbrüggen reaction could be employed to convert the pyranose ring into the desired furanose nucleoside **12**. Finally, oxidation of the thioether and thermolysis of the resulting sulfilimine could install the required C2−C3 dehydrofuranose moiety present in **1**. The success of this strategy hinged on the accessibility of optically enriched (*S*)-**3**. Similar structural pyranone derivatives have demonstrated broad utility as versatile building blocks in organic synthesis,[5] and as key components in the development of new synthetic methods.[6] However, all previous approaches to (*S*)-**3** and similar derivatives suffered from unsatisfactory yields,[7] and required the use of either chiral chromatography, derivatization, or enzyme-mediated resolution to impart high enantiopurity. Our previously published work (Scheme 1a) employed an enzymatic resolution by destructive transesterification to deliver (*S*)-**3a** in high purity and enantioselectivity, but in moderate overall yield (26% from **2a**).[8]

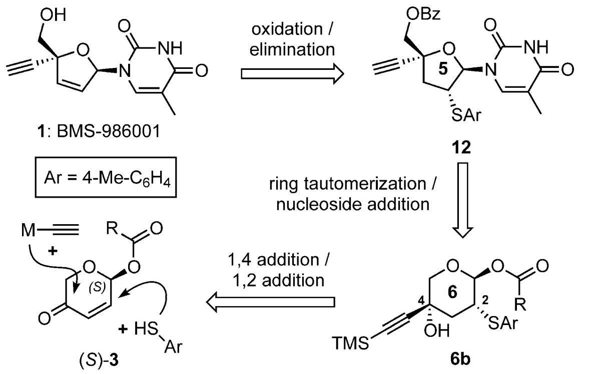

Figure 1. Retrosynthetic analysis of BMS-986001 (**1**). Bz = benzoyl.

To increase both efficiency and overall yield, a dynamic kinetic asymmetric transformation (DYKAT) was considered for the acylation of the racemic lactol **2a** (Scheme 1b). Limited precedence existed for this transformation biocatalytically, and most reports achieved only low to moderate enantioselectivity.[9] In fact, in our hands, screening of more than 100 enzymes led to either the undesired isomer [(*R*)-**3a**][10] or (*S*)-**3a** with low selectivity. Despite the emergence of a number of catalysts shown to resolve secondary alcohols by way of non-enzymatic selective acylations,[11] to the best of our knowledge, there have been no reports of a small molecule facilitating this important transformation on a lactol. An initial screen of organocatalysts resulted in low levels of conversion and/or selectivity. Surprisingly, the best result was achieved using levamisole (**A**), an inexpensive and

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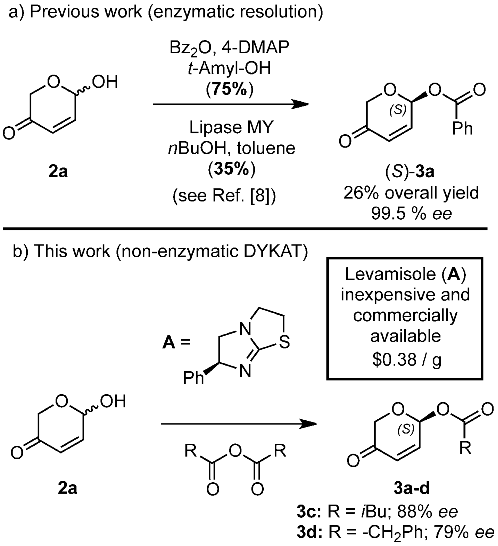
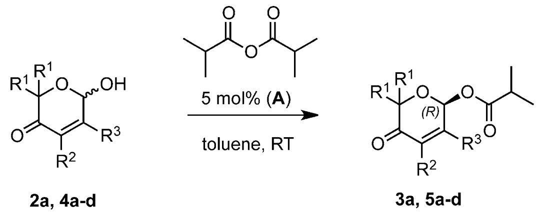


Scheme 1. Synthetic routes to (*S*)-**3** by enzymatic resolution (a) and by non-enzymatic DYKAT (b). DMAP = 4-(*N*,*N*-dimethylamino)pyridine.

Table 2: Levamisole-mediated DYKAT of the selected pyranose lactols **2a** and **4a–d**.[a]



Starting material	Product	R^1	R^2	R^3	Yield [%][b]	*ee* [%][c]
2a	**3c**	H	H	H	91	88
4a	**5a**	Me	H	H	91	86
4b	**5b**	H	Me	H	90	82
4c	**5c**	H	H	Me	96	72
4d	**5d**	H	H	Ph	96	55

[a] Reaction conditions: levamisole (0.05 equiv), isobutyric anhydride (1.2 equiv), 20 mL toluene/g substrate, 1 h, RT. [b] Determined after isolation by chromatography. [c] Determined by HPLC analysis on a chiral stationary phase.

commercially available small molecule (Scheme 1 b; for details see Table 1), which currently has found only limited utility in kinetic resolutions.[12]

Optimization of this transformation ensued with the use of Bz_2O (Table 1, entry 1), which we found to be suboptimal, thus confirming previous reports.[13] This shortcoming prompted us to explore alternative alkyl anhydrides, resulting in increased reaction rates, albeit with modest enantioselectivities (entries 2 and 3; 60–70 % *ee*). Employment of a nonpolar solvent (toluene) and isobutyric anhydride allowed us to achieve our highest level of enantioenrichment (entry 4). However, the acylated product **3c** was noncrystalline, thus preventing further enantioenrichment by crystallization. Fortunately, the crystalline phenylacetate derivative **3d** provided similar initial selectivity (79 % *ee* crude) with the benefit of further enrichment by crystallization (99 % *ee*), a small compromise which enabled its preparation on multigram scale (entry 5) from racemic **2a**.

Table 1: Optimization of the levamisole-mediated DYKAT of **2a** (see Scheme 1 for reaction equation).[a]

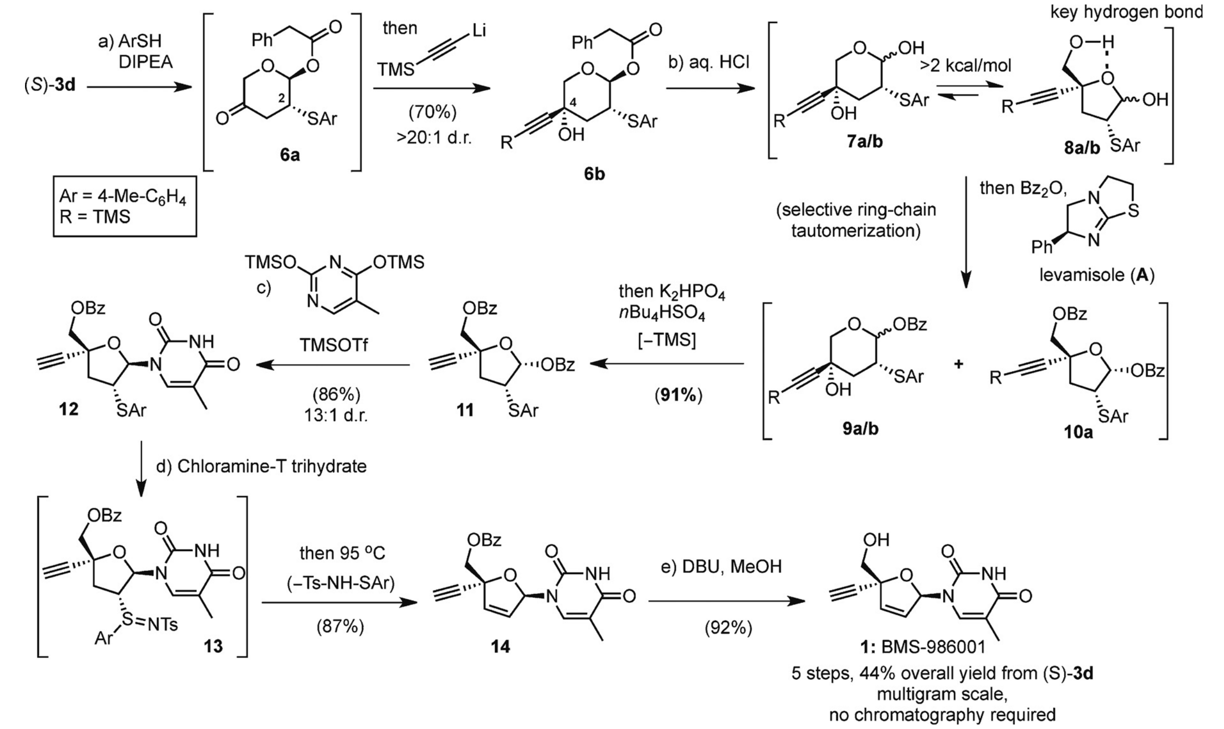
Entry	R	3	Solvent	Conv. [%][b]	*ee* [%][c]
1	Bz	**3a**	*t*-amyl alcohol	60	33
2	Ac	**3b**	*t*-amyl alcohol	> 95	60
3	CH_2Ph	**3d**	*t*-amyl alcohol	> 80	60
4	*i*Pr	**3c**	toluene	> 95	88
5[a]	CH_2Ph	**3d**	toluene	> 95	79

[a] Reaction conditions: levamisole (0.05 equiv), anhydride (1.2 equiv), 10 mL solvent/g substrate, 1 h, RT. [b] Determined by HPLC analysis. [c] Determined by HPLC analysis on a chiral stationary phase.

While extremely pleased with the DKR results on **2a**, we were curious about the scope of this important and previously unprecedented transformation (Table 2). Similar acylated pyranose lactols have been broadly utilized as chiral building blocks in organic chemistry and have functioned as starting materials in numerous total syntheses.[5] Application of the optimized reaction conditions to a series of substituted pyranose lactols (**4a–d**) demonstrated good tolerance for alkyl substitution at C2 (**4c**→**5c**), C3 (**4b**→**5b**), and C5 (**4a**→**5a**). While aryl substitution at C2 (**4d**→**5d**) led to reduced enantioselectivity (55 % *ee*), the high yield and crystallinity of the product still enabled a practical alternative (> 99 % *ee* after recrystallization from methyl *tert*-butyl ether) to enrichment by chiral chromatography. Further studies and mechanistic understanding of this transformation are currently under investigation.

With a preparation of enantiopure (*S*)-**3d** secured, we proceeded with its utilization in the synthesis of **1** as outlined in Scheme 2. Diastereoselective thioconjugate addition of *p*-thiocresol with (*S*)-**3d** resulted in the C2 sulfide **6a** (> 50:1), which was immediately reacted with lithio-TMS-acetylene (−78 °C) in a single-pot operation to afford the crystalline pyranose **6b** in high yield and selectivity (70 % yield, > 20:1 d.r.). Installation of the aryl sulfide at this juncture was designed to play a critical role throughout the synthesis, thus acting as a relay for stereochemical information. With the crucial remote C4 stereocenter successfully installed, we proceeded to confront what would be one of the most challenging transformations in the synthesis: selective pyranose to furanose ring-chain tautomerization (**6b**→**11**).

Carbohydrate ring-chain tautomerization is known to be substrate-dependent and effected by a number of external variables (i.e., solvent, pH, temperature, and pressure).[14] Although initially discouraged by literature accounts describing the general preference of carbohydrates to exist in the pyranose form,[15] we were hopeful a solution would be discovered. Initial hydrolysis of **6b** (aq. HCl, CH_3CN, 20 °C, 10 h) provided access to the furanose form **8a/b**, but also vastly increased the complexity of the system by generating a rapidly equilibrating mixture of four lactol isomers (**7a/b**↔**8a/b**). ^1H NMR studies conducted on this lactol mixture revealed a mild preference for the furanose form in nonpolar solvents ([D_6]benzene = 60 % versus CD_3CN = 5 %), presum-



Scheme 2. Synthesis of BMS-986001 (**1**) from (*S*)-**3d**. Reagents and conditions: a) *p*-thiocresol (1.1 equiv), *i*Pr_2EtN (0.05 equiv), toluene, 20°C, 30 min, then lithio-TMS-acetylene (2.5 equiv), THF (3.0 equiv), −78°C, 1 h, 70%; b) 1 N HCl (0.5 equiv), CH_3CN/H_2O (5:1), 20°C, 10 h, then Bz_2O (3.0 equiv), levamisole (0.1 equiv), toluene, 20°C, 48 h, then K_2HPO_4 (3.0 equiv), *n*Bu_4HSO_4 (0.2 equiv), H_2O (3.0 equiv), toluene, 0°C, 1.5 h, 91%; c) bis(TMS)thymine (1.4 equiv), TMSOTf (1.4 equiv), CH_3CN, 10 to 20°C, 4.5 h, 86%, (13:1 d.r.); d) Chloramine-T (1.2 equiv), AcOH (0.1 equiv), CH_3CN, 20°C, 2.5 h, then *n*BuOH, 95°C, 3 h, 87%; e) DBU (0.05 equiv), MeOH, 60°C, 15 h, 92%. DBU = 1,8-diazabicyclo[5-4-0]undec-7-ene, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran, TMS = trimethylsilyl, Ts = 4-toluenesulfonyl.

ably because of a key hydrogen bond between the ring oxygen atom and the C5 hydroxy group.[16] The discovery of this solvent effect on the tautomer equilibrium prompted us to replace CH_3CN with toluene prior to advancing. Extensive optimization of the selective benzoylation, led to the discovery that **8a/b** could be trapped as its bis(benzoate) derivative (**10a**) using levamisole (10 mol%, Bz_2O, toluene, 20°C, 48 h) as a nucleophilic organocatalyst. These reaction conditions resulted in remarkable selectivity (98:2, furanose/pyranose, > 50:1 α:β), and facilitated a highly successful ring-chain tautomerization transformation. After mild and selective hydrolytic removal of the TMS group (K_2HPO_4, *n*Bu_4NHSO_4, H_2O, toluene, 0°C), the crystalline α-Bz-furanose 11 was isolated in 91% overall yield from **6b**. Next, a Vorbrüggen reaction with bis(TMS)thymine furnished the nucleoside **12** in 86% yield and with high β-selectivity (13:1 d.r.), presumably influenced by the presence of the C2 aryl sulfide.[17] The nucleoside **12** was then converted into the dehydrofuranose **14** through a one-pot, two-step procedure involving selective Chloramine T[18] mediated sulfur oxidation to give the corresponding sulfilimine **13** followed by thermolysis under relatively mild reaction conditions (95°C, 3 h, 87% yield). At this point, the crucial role of the C2 aryl sulfide becomes clear: initially, it provided conformational control and relayed facial selectivity guiding the introduction of the C4 acetylene (**6a**→**6b**), later it provided assistance governing the β-selective nucleoside addition (**11**→**12**), and now it has served as a handle for the installation of the dehydrofuranose backbone (**12**→**14**). Finally, HIV-inhibitor BMS-986001 (**1**) was obtained in excellent yield (92%) through a DBU-catalyzed transesterification.

In summary, we have demonstrated a novel and highly efficient synthesis of BMS-986001 (**1**) in five steps and 44% overall yield from (*S*)-**3d**. Highlighted in this work is the unexpected utility of the inexpensive and readily available organocatalyst, levamisole (**A**), first as a means to prepare enantiomerically enriched building block (*S*)-**3d** (by an unprecedented non-enzymatic DYKAT of lactol **2a**), and later as a highly effective catalyst facilitating the ring-chain tautomerization of a pyranose into a furanose (**6b**→**11**). Complete studies regarding the development of these levamisole-mediated transformations, along with an account covering the application of this chemistry in the preparation more than 250 kg of **1** will be disclosed in due course.[19]

Keywords: inhibitors · kinetic resolution · organocatalysis · synthesis design · tautomerism

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