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Multi-gram synthesis of a nucleotide-competing reverse transcriptase inhibitor

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ABSTRACT

An efficient multi-gram synthesis of a nucleotide-competing reverse transcriptase inhibitor is reported. The synthesis features a chiral auxiliary-assisted alcohol resolution, a Mitsunobu reaction involving a carbamate, followed by a lithium-iodide exchange/Weinreb ketone synthesis tandem. These chemical transformations were optimized in order to increase the yield of the synthesis. The route is concluded by a late-stage palladium-catalyzed cyanation followed by a pyrimidine-2-one ring formation.

1. Introduction

According to the World Health Organization, an estimated 34 million people were infected with HIV worldwide in 2010, mostly in Sub-Saharan Africa.[1] Fortunately, progress in highly active antiretroviral therapy over the past 20 years has reduced the mortality caused by the AIDS epidemic.[2] While a vaccine cure aimed at the eradication of the disease is the most desirable goal, supplementing the antiviral arsenal with novel drugs aiming at highly validated viral targets is also needed. In particular, inhibition the HIV reverse transcriptase is a key component in reducing viral load and suppressing the infection.[3]

Our research group focused on a new class of reverse transcriptase inhibitors, nucleotide-competitive reverse transcriptase inhibitors (NcRTIs).[4] These non-nucleosidic molecules bind at, or very close to, the active site of the enzyme,[5] thereby competing with incoming deoxyribonucleotide triphosphates (dNTP). This mode of inhibition prevents elongation of the proviral DNA strand, but does not lead to chain termination. As such, NcRTIs could complement currently available NRTI and NNRTI regimens, especially in the context of the emergence of drug-resistant HIV strains.

Following a high-throughput screening campaign, a new chemotype exhibiting NcRTI mechanism was discovered. Extensive lead optimization led to the discovery of inhibitor **1** that demonstrated excellent antiviral potency, favorable cross-resistance profile, and good pharmacokinetic profile. Based on its favorable in vitro and in vivo profiles, this molecule was selected as a candidate for toxicological and pharmacological studies, requiring a multi-gram synthesis of the active pharmaceutical in high purity. However, the highly functionalized polycyclic molecule **1** posed several synthetic challenges (Fig. 1). Starting from azabenzofuran **2**, the following chemical steps were required: mono-coupling of pyrazole at the C-8 position, cyanation at position C-7, introduction of optically pure 2-ethyltetrahydropyran-4-yl at N-1, without erosion of stereochemical integrity, and introduction of an *N*-methylpyrazole at the C-4 position. The present communication describes the optimization of these key transformations, leading to the multi-gram synthesis of **1**.

2. Synthesis of optically pure tetrahydropyran 4

In order to develop an efficient synthesis of tetrahydropyran alcohol **4**, we decided to embark on a racemic synthesis followed by a chiral auxiliary-assisted separation. Strict timelines, combined with synthetic challenges and the need for a high level of optical purity (>98.5% ee) precluded the pursuit of a stereoselective synthesis.

The epimer of alcohol **4** (***epi*-4**) was prepared using a Prins reaction between propionaldehyde and 3-buten-1-ol, according to a previously reported procedure, in good yield (Scheme 1).[6] The *cis* diastereomer was obtained with 95:5 selectivity; the undesired *trans* isomer could be removed by chromatography during the enantioresolution process (vide infra). The stereochemistry of ***epi*-4** at the alcohol center had to be inverted to obtain the desired

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† This article is dedicated to the memory of Dr. Louis Morency (1979–2012), fellow scientist, colleague and friend.

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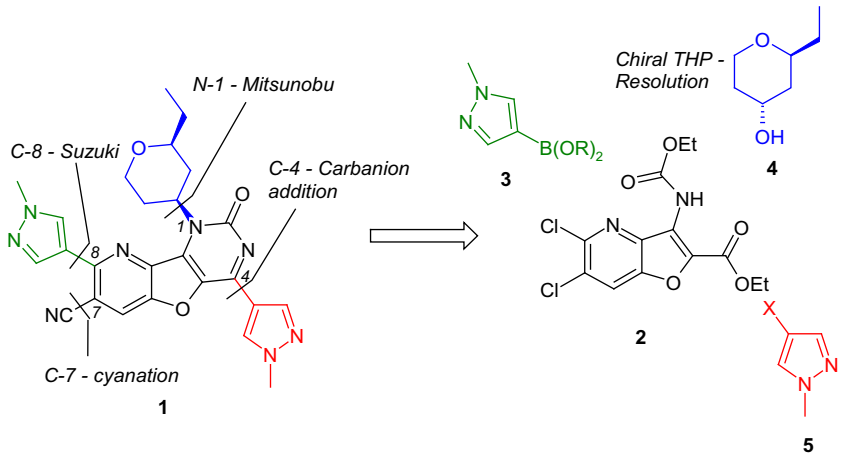
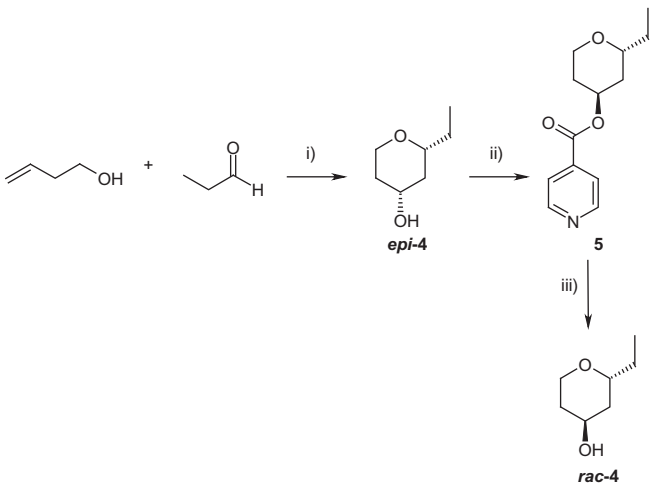


Figure 1. Retrosynthetic approach to compound **1**.

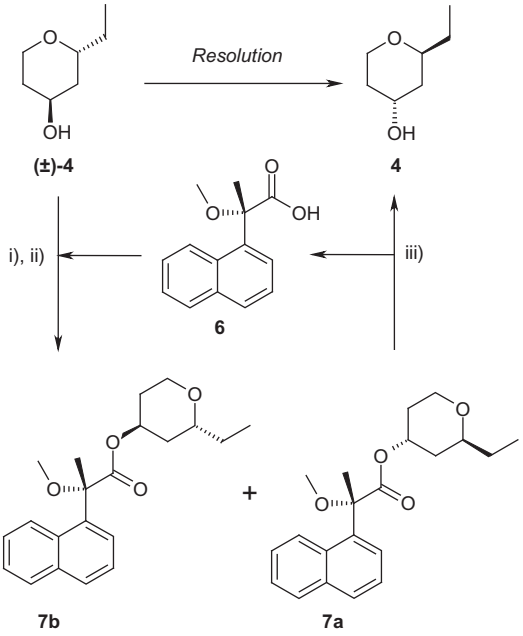
stereochemical outcome in the subsequent Mitsunobu reaction involving carbamate **2** (vide infra). To this end, a Mitsunobu reaction with isonicotinic acid led to complete inversion of stereochemistry. A simple two-step acid–base extraction was performed, affording compound **5**. Isonicotinate ester **5** was hydrolyzed under basic conditions followed by vacuum distillation to afford hydroxypyran ***rac*-4** as a racemic mixture.

We planned on obtaining optically pure tetrahydropyran **4** through chromatographic separation after coupling of a chiral auxiliary. Several chiral auxiliaries (amino acids, Mosher's ester, Trost's ester) were screened, but no practical level of separation of the enantiomeric mixture could be achieved. Finally, Harada's chiral auxiliary **6** was selected for its demonstrated enantioresolution capability[7] (Scheme 2). Due to the fact that the element imparting chirality is far removed from the chiral auxiliary, the separation of **7a** and **7b** proved challenging using standard 40–63 μm silica. However, the diastereomeric mixture comprising **7a** and **7b** was successfully separated with the help of medium-pressure chromatography, using high performance silica cartridges.[8]

After cleavage of the ester under basic conditions, an acid–base separation was performed, at which point chiral auxiliary **6** was isolated and recycled, with recovery greater than 80%. The optically pure tetrahydropyran was obtained in good yield, typically between 60% and 70%.



Scheme 1. Synthesis of ***rac*-4**. Reagents and conditions: (i) H_2SO_4; 80%; (ii) isonicotinic acid, triphenylphoshine, DIAD, THF; (iii) NaOH, MeOH; >90% (two-steps).



Scheme 2. Enantioresolution of chiral tetrahydropyran **4**. Reagents and conditions: (i) DCC (1.1 equiv), DMAP (0.5 equiv), CSA (0.1 equiv), DCM; (ii) separation of diastereomers (highly spherical silica), 25:75 EtOAc:Hex; (iii) NaOMe, 70 °C, then water, 80 °C; 60–70% yield.

The absolute configuration of **4** was determined by comparison of the ^{1}H NMR spectral data of compounds **7a** and **7b**. Chiral auxiliary **6** is known to induce strong, unambiguous anisotropic shifts. In the case of **7a** and **7b**, $\Delta\delta$ values were consistent with (2*S*,4*R*) and (2*R*,4*S*) configurations, respectively.[7,9]

3. Study of the Mitsunobu reaction

The Mitsunobu reaction represents an efficient way of creating carbon–heteroatom bonds with complete preservation of optical purity.[10] This transformation was clearly the procedure of choice