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The synthesis of tetrahydropyridopyrimidones as a new scaffold for HIV-1 integrase inhibitors

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Abstract—An efficient synthesis of methyl 9-amino-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate as a late stage intermediate for a new class of HIV-1 integrase inhibitors is described. After construction of the bicyclic core scaffold, a stereoselective introduction of the chiral amino group in the 9-position is achieved.

We have previously reported on *N*-methyl-5-hydroxypyrimidone carboxamides as potent HIV-1 integrase inhibitors, of which compound **A** (Fig. 1) is a representative example.[1] During the SAR exploration of these inhibitors, one of our efforts concentrated on fused bicyclic analogs **B** shown in Figure 1. Herein we report on the synthesis of tetrahydropyridopyrimidone **C** (Fig. 2) as a versatile precursor for HIV-1 integrase inhibitors of type **B**.[2]

Our retrosynthetic analysis for **C** is shown in Figure 2. We envisioned the installation of the chiral methylamino group in the 9-position after the formation of the core scaffold in order to avoid racemization during the cyclization step which occurs at elevated temperatures or in the presence of a strong base. In general, 2-carboxy-3,4-dihydroxy-pyrimidines can be obtained by two methods: either by a condensation reaction between amidines and dihydroxyfumarate derivatives **3**[3] or by a reaction of amidoximes with dimethylacetylene dicarboxylate (DMAD).[4]

Cyclic amidines **2** (Route 1, Fig. 2) or cyclic amidoxime **4** (Route 2, Fig. 2) seemed attractive starting materials to us because of the convergent formation of the tetrahydropyridopyrimidone bicycle in one step. The use of these cyclic analogs was unprecedented though and the feasibility of both routes had to be explored. Route 1 (Scheme 1) started with the synthesis of the benzyl protected dimethyldihydroxyfumarate **3a** by a Claisen condensation of methyl benzyloxyacetate and dimethyl oxalate as described previously.[3] The crude material **3a**

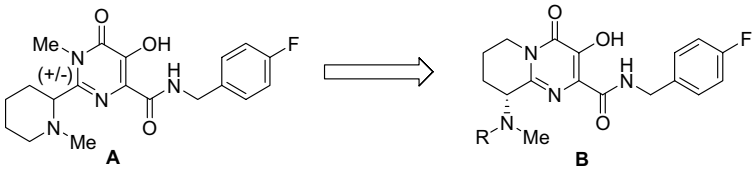

Figure 1.

Keywords: Tetrahydropyridopyrimidone; Integrase inhibitor; 1,2,4-Oxadiazoline; Amidoxime.
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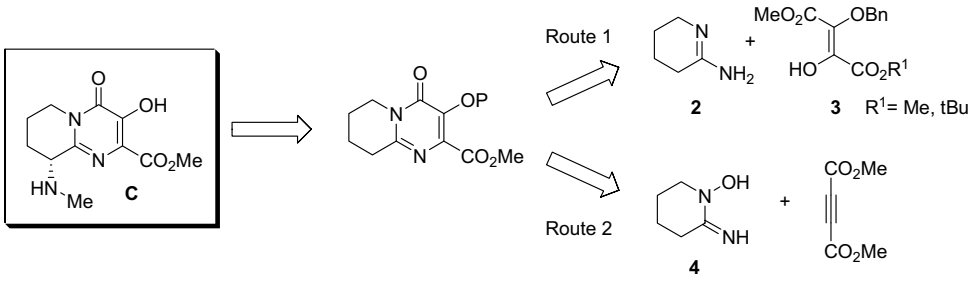
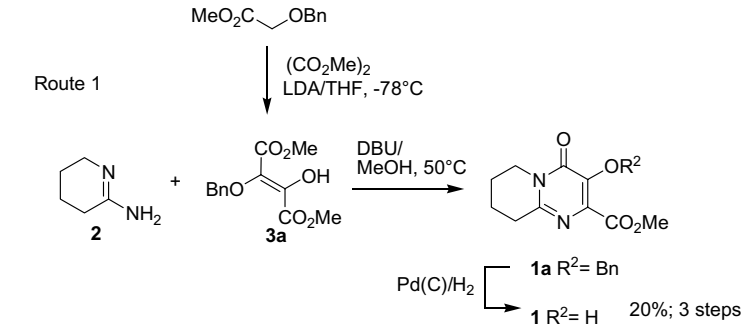
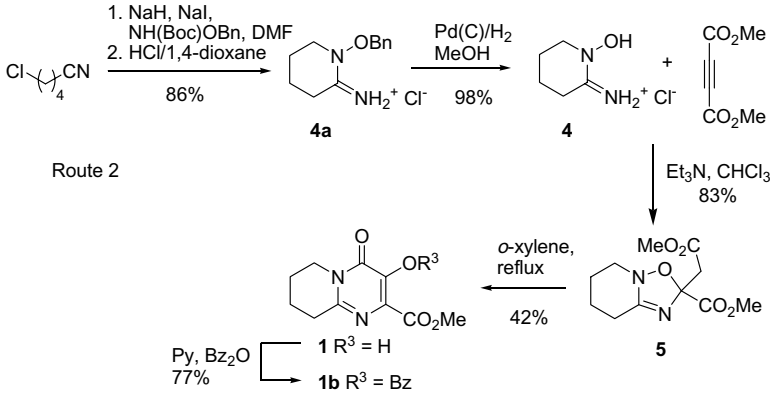


Figure 2.



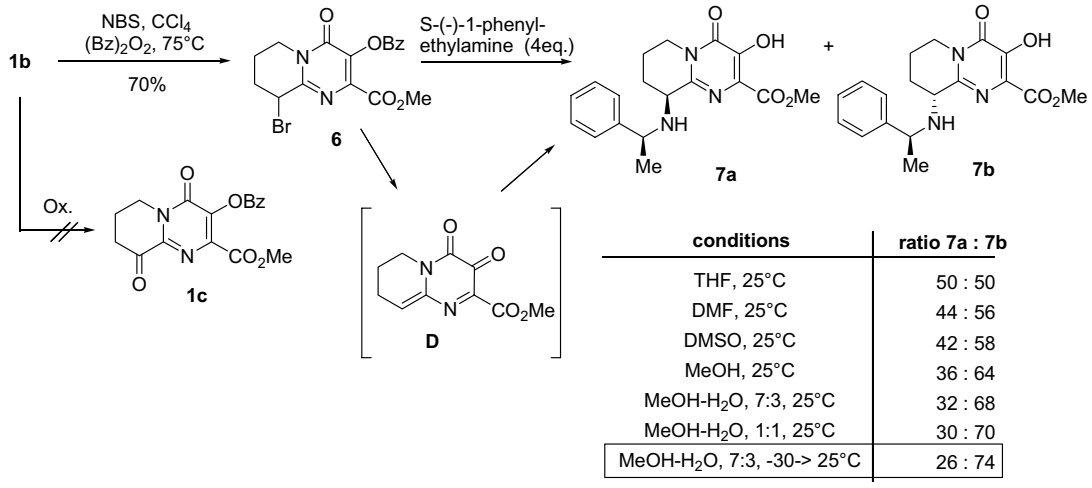
Scheme 1.



Scheme 2.

was employed in a condensation reaction with the commercially available cyclic amidine **2**, using DBU as base in methanol at 50 °C. After cleavage of the benzyl ether by hydrogenation, tetrahydropyridopyrimidone **1** was obtained in a 20% yield. To explore the alternative Route 2 (Scheme 2), the cyclic amidoxime **4** had first to be prepared. This was achieved efficiently in a three step sequence by alkylation of *N*-Boc-*O*-benzyl hydroxylamine with 4-chlorovaleronitrile,[5] then treated with 4 M HCl in 1,4-dioxane which promoted Boc-cleavage and a subsequent in situ cyclization to **4a**. Finally, cleavage of the benzyl ether by hydrogenation afforded **4** in high yield. 1-Hydroxypiperidin-2-iminium chloride **4** readily reacted with DMAD in chloroform in the presence of one equivalent of base. The formed adduct was determined as the bicyclic 1,2,4-oxadiazoline **5**.[6] Heating to reflux in *o*-xylene for 5 h promoted ring-opening and subsequent thermal rearrangement/cyclization to tetrahydropyridopyrimidone **1** which was isolated in 42% yield. The 3-hydroxyl group of **1** was protected as a benzoic ester in order to increase the solubility in non-protic solvents. Route 2 was used for the preparation of multigram quantities of intermediate **1b**.

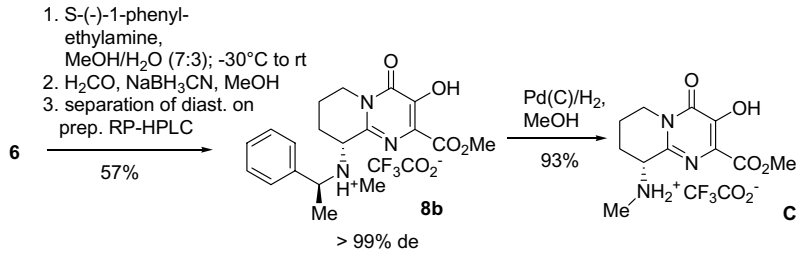
Next, the installation of the amino group in position 9 had to be accomplished, ideally in an enantioselective fashion. Our first intent to prepare the 9-oxo-analog **1c** as an useful intermediate for an enantioselective synthesis was hampered by the difficulty to cleanly oxidize **1b** (Scheme 3). Reagents like PDC, PCC, CrO_3, MnO_2 or $KMnO_4$ gave either low conversion or degradation. An alternative approach was found by bromination of **1b** with NBS under radical conditions as described previously.[1] The resulting bromo-intermediate **6** was



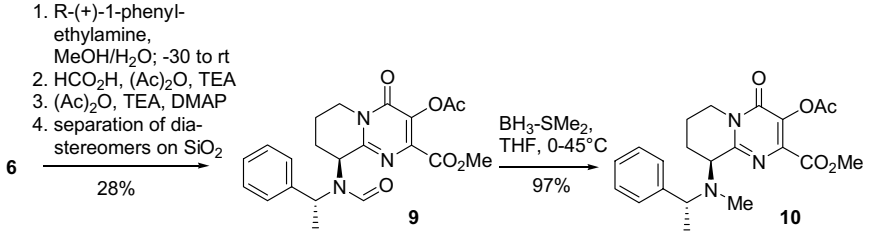
Scheme 3.

subjected to a reaction with (*S*)-(−)-1-phenylethylamine in DMF to give a pair of diastereomeric amines **7a** and **7b**. Interestingly, this reaction proceeded with a slight diasteromeric excess (44:56, Scheme 3) and screening for conditions to further increase the diastereoselectivity was undertaken. The best result (48% de) was obtained when the reaction was carried out in a MeOH–water mixture (7:3) at −30 °C with an excess of the chiral amine (Scheme 3). Polar protic solvents and low temperatures increased the diastereoselectivity. We believe that the first step in the reaction of **6** with (*S*)-(−)-1-phenylethylamine is O-deprotection, since products containing the benzoic ester were never observed. In the presence of an excess of amine HBr can eliminate to form a reactive *p*-quinone-like structure **D** as an achiral intermediate (Scheme 3). After methylation of the amino group the separation of the two diastereomers **8a** and **8b** was performed by preparative RP-HPLC. The final step was the cleavage of the chiral auxiliary by catalytic hydrogenation. Using this procedure the versatile intermediate **C** could be prepared in 53% yield from racemic **6** (Scheme 4).

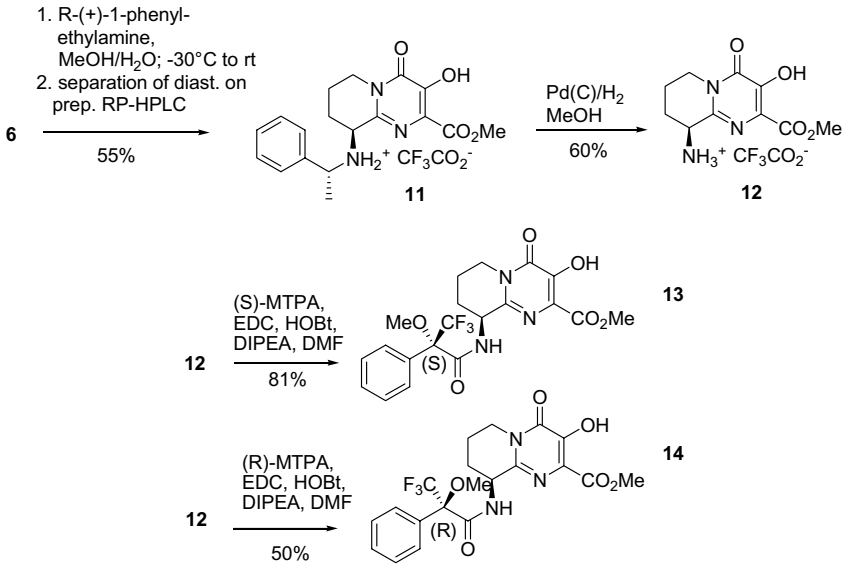
Since the separation of **8a** and **8b** by RP-HPLC was time consuming, an alternative procedure for the separation of the diastereomers either by crystallization or by chromatography on silica gel was sought. Attempts to enrich the mixture of diastereomers by crystallization were unsuccessful and our attention turned to a separation by silica gel chromatography. For this purpose the amino and the hydroxyl group had to be protected with groups whose removal should proceed without loss of enantiomeric purity. After several attempts to protect the amino group of **7a**/**7b** as amides or carbamates, the route shown in Scheme 5 was found to be a practical solution. After the diastereoselective reaction of **6** with the chiral amine the intermediate was formylated on the secondary amine and acetylated on the hydroxy group (the corresponding formic ester was labile towards hydrolysis). The obtained mixture of diastereo-



Scheme 4.



Scheme 5.



Scheme 6.

mers separated well by silica gel chromatography and a subsequent reduction of the formamide to a methyl amine by borane–dimethylsulfide furnished intermediate **10** without loss of enantiomeric purity. The absolute configuration of **12** (Scheme 6, using *R*-(+)-1-phenylethylamine) was determined by derivatization with the two enantiomers of the chiral reagent MTPA and comparison of the chemical shifts of the resulting diastereomers. Energy assessment on the MTPA amides using molecular mechanics and semiempirical (AM1) calculations, together with careful examination of aromatic shielding and deshielding effects on the substituents in position α to the amine, indicated a configuration of *S* at the chiral center in **12**.[7]

In summary, an efficient synthesis of the new heterocyclic ring system methyl 3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate has been achieved. The installation of a chiral amino group in the 9-position has been performed after the cyclization step in a stereoselective fashion using a racemic bromo-intermediate as starting material.

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Supplementary data

Experimental procedures and spectral data of the products as well as details regarding the determination of the absolute configuration of **12**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.07.043.

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