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A highly diastereoselective chloride-mediated dynamic kinetic resolution at phosphorus on-route to a key intermediate in the synthesis of GSK2248761A

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ABSTRACT

A highly diastereoselective chloride-mediated dynamic kinetic resolution at phosphorus has been developed to access a key intermediate in the synthesis of GSK2248761A. This procedure utilises a soluble chloride source and a cheap readily available chiral auxiliary. The practicality of this transformation is demonstrated on a multi-gram scale.

GSK2248761A (Fosdevirine, IDX-899) **1** is an experimental Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) discovered by Idenix Pharmaceuticals and was in development for the treatment of HIV (Fig. 1).[1] During our investigations towards an efficient scalable synthesis of **1** we desired an asymmetric synthesis to the key intermediate **2**, which we could insert into our current synthetic route.[2] We discovered that there were only a few methods to construct optically active phosphinate esters using techniques other than a classical resolution.[3] Mislow and co-workers first described the use of (−)-menthol as a chiral auxiliary that allowed the separation of diastereomers by fractional crystallization followed by further elaboration to optically active phosphine oxides and phosphinates.[4] We were able to prepare and separate by chromatography diastereomerically enriched menthyl phosphinate esters **3** and **4**, but our substrate proved unstable to the harsh transesterification conditions required to convert it into the desired methyl phosphinate (Fig. 2).[5] Jennings and co-workers reported the synthesis of optically active *P*-phenyl-*P*-(2,4,6-trimethylphenyl)-phosphinamide *via* a (−)-(1*R*)-*N*-(1-phenylethyl)-(S_P)-*P*-phenyl-*P*-(2,4,6-trimethylphenyl)phosphinamide where a partial kinetic resolution was observed (Scheme 1).[6] Based on Jennings' observations we decided to pursue the synthesis of *P*-optically active phosphinate ester **2** *via* a diastereomerically enriched phosphinamide leading to the discovery of an efficient dynamic kinetic resolution process at phosphorus.

Our previously reported synthesis of GSK2248761A generated multi-kilo quantities of the racemic methyl phosphinate ester **8** that could be easily converted into the phosphinic acid **9** (Scheme 2). Treatment of the ester **8** with lithium chloride in DMSO at 60 °C furnished the desired phosphinic acid **9** in 81% yield on a 15 kg scale. It was essential to sweep the methyl chloride produced away from the headspace for the reaction to proceed to completion.

The phosphinyl chloride **10** was synthesized *in situ* using oxalyl chloride in dichloromethane to provide material for scoping studies. Repetition of the Jennings' conditions only gave a 1:1 mixture of diastereomers, even under a number of alternative solvent conditions (Scheme 3). Operating the reaction at a lower temperature also failed to change this ratio. Moreover, when a single diastereomer was separated by flash chromatography and reacted with hydrochloric acid in MeOH to give the methyl phosphinate ester **13** some epimerization at phosphorus was observed to give a 75% *e.r.*[7] It was found that the epimerization could be avoided by switching to concentrated sulfuric acid as the acid source. It was not clear at this stage what the role of the acid counter ion was in the epimerization (*vide infra*).

A screen of commercially available chiral amines as auxiliaries was performed in THF (Table 1, entries 1–8). The highest diastereoselectivity and reactivity in our initial screen was achieved using the phenyl glycinamide derivative **15** (Entry 1). A sample after 3 h revealed an erosion of the diastereoselectivity as the reaction proceeded towards completion suggestive of a dynamic kinetic resolution. We

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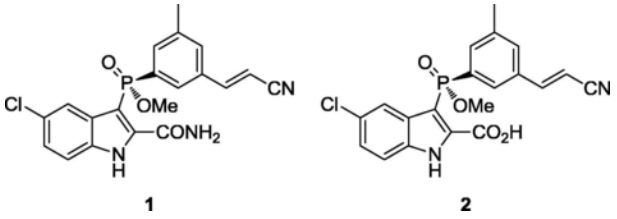


Fig. 1. Structure of GSK2248761A and **2**.

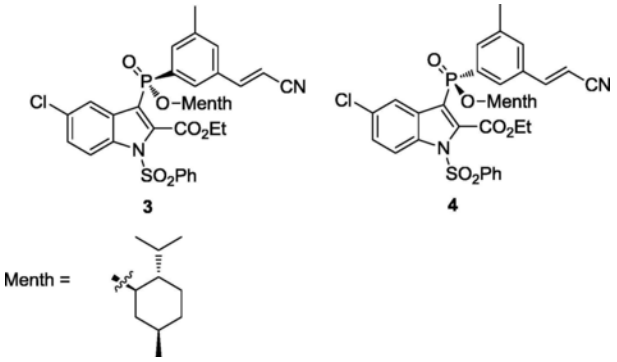
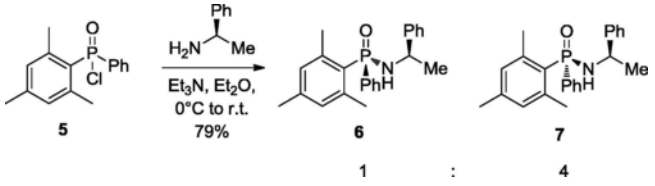
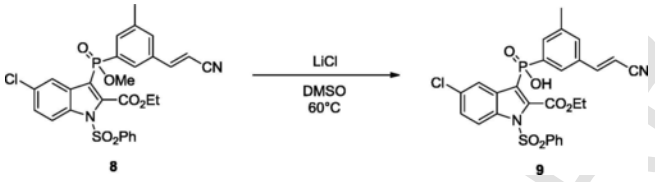


Fig. 2. Diastereomeric (−)-Menthyl phosphinate esters prepared analogous to Mislow and co-workers.



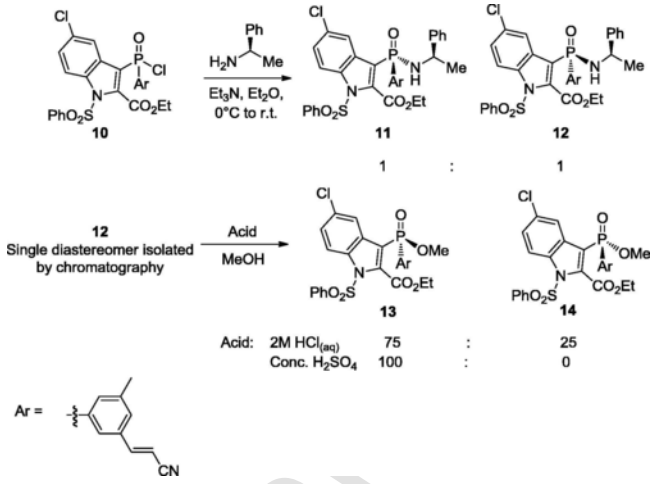
Scheme 1. Jennings DKR at phosphorus utilizing (*R*)-1-phenylethylamine.



Scheme 2. LiCl mediated demethylation of the phosphinic ester **8**.

followed this interesting result with a screen of bases and additives to try to maintain the higher *d.r*. throughout (Entries 9–13). We observed that the base had virtually no effect on diastereoselectivity. However, there was a striking difference upon the addition of LiCl (Entry 13), which enabled the high diastereoselectivity to be maintained throughout. We speculated that the external chloride source was acting by rapid nucleophilic attack at the phosphorus centre of the phosphinyl chloride **10**, thereby racemising the stereocentre in the starting material. The screen of commercially available chiral amines was expanded under more optimal conditions (Entries 14–20). The highest diastereoselectivity (91:9) was achieved with (*S*)-phenyl glycine methyl ester **25**, used as the hydrochloride salt to maintain chiral integrity of **25** throughout the reaction (Entry 16).

When the reaction was scaled up to 2 g the *d.r.* dropped to 85:15. We speculated that the reduction in *d.r.* was due to poor mass transfer of LiCl, which when replaced with the more soluble tetra-*n*-butylammonium chloride (TBAC) restored the diastereoselectivity to 91:9



Scheme 3. Initial scoping reactions utilizing (*R*)-1-phenylethylamine as a chiral auxiliary.

(Table 1, entry 21). The reaction conditions were optimized further by selecting tetra-*n*-octylammonium chloride in toluene at 0–5 °C to give a *d.r*. of 95.5:4.5 in solution at the end of the reaction (Scheme 4, see ESI for optimization details). The product was isolated by crystallization from toluene-heptane in 81% yield, which upgraded the *d.r*. to >95:5 on a 10 g scale.

The methanolysis was performed using 10 equivalents of methanesulfonic acid in methanol as it was found that the use of concentrated sulfuric acid led to low levels of the hydrolysis product **9** (Scheme 4). It was also observed that the use of methanesulfonic acid was preferred over hydrochloride acid to maintain the chiral integrity of the phosphorus centre in product **31**. Presumably the nucleophilic nature of the chloride counter-ion in hydrochloric acid promotes inversion of the chiral centre at phosphorus, *via* a similar mechanism to that exploited in the DKR stage of this synthetic process. Switching to the non-nucleophilic methanesulphonate counter-ion appears to avoid this undesirable reaction.

In order to intercept our current synthetic route we needed to cleave the benzenesulfonate protecting group and hydrolyse the methyl ester to the carboxylic acid. This was accomplished using aqueous sodium hydroxide in acetonitrile to generate a solution of the acid **2**. This solution of the acid was treated with Cinchonidine in ethyl acetate to form the diastereomeric salt in 99% *d.r.* and 76% overall yield from **30** on 10 g scale.

In summary, we have developed the first scalable example of a highly diastereoselective chloride mediated dynamic kinetic resolution of a phosphinate ester. The route accomplishes the synthesis of the chiral phosphinate ester **31** in 50% overall yield from the methyl phosphinate ester **8** with greater 99%a/a HPLC purity and 99% *e.r*. The strategy offered an alternative approach to classical resolution and expands the scope of this useful reaction.

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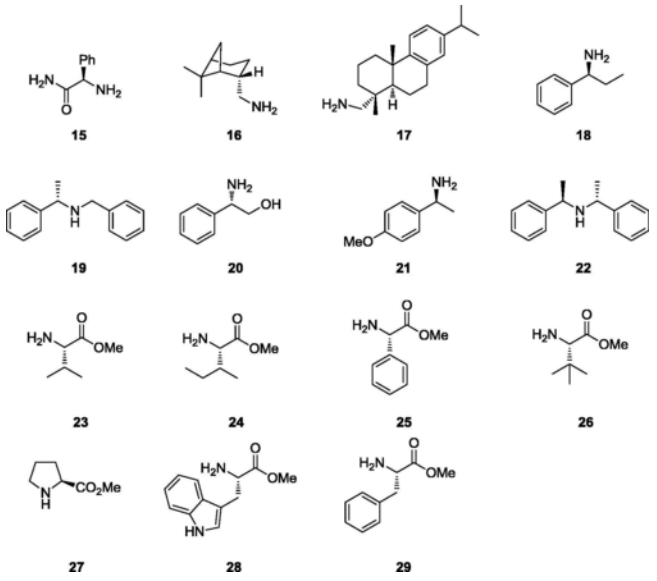
A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.04.018.

Table 1
Screening of chiral amines in a kinetic resolution.



Entry	Amine[a]	Base	Additive	*d.r.*[b]
1	**15**	Et_3N	–	61:39 (74:26)[c]
2	**16**	Et_3N	–	53:47
3	**17**	Et_3N	–	50:50
4	**18**	Et_3N	–	56:44
5	**19**	Et_3N	–	n.d.[d]
6	**20**	Et_3N	–	65:35
7	**21**	Et_3N	–	56:44
8	**22**	Et_3N	–	n.d.[d]
9	**15**	DABCO	–	68:32
10	**15**	DBU	–	n.d.[d]
11	**15**	DMAP	–	48:52
12	**15**	Imidazole	–	n.d.[d]
13	**15**	Et_3N	LiCl	75:25
14	**23**	Et_3N	LiCl	75:25
15	**24**	Et_3N	LiCl	72:28
16	**25**	Et_3N	LiCl	91:9
17	**26**	Et_3N	LiCl	87:13
18	**27**	Et_3N	LiCl	n.d.[d]
19	**28**	Et_3N	LiCl	77:23
20	**29**	Et_3N	LiCl	n.d.[d]
21	**25**	Et_3N	TBAC	91:9[e]

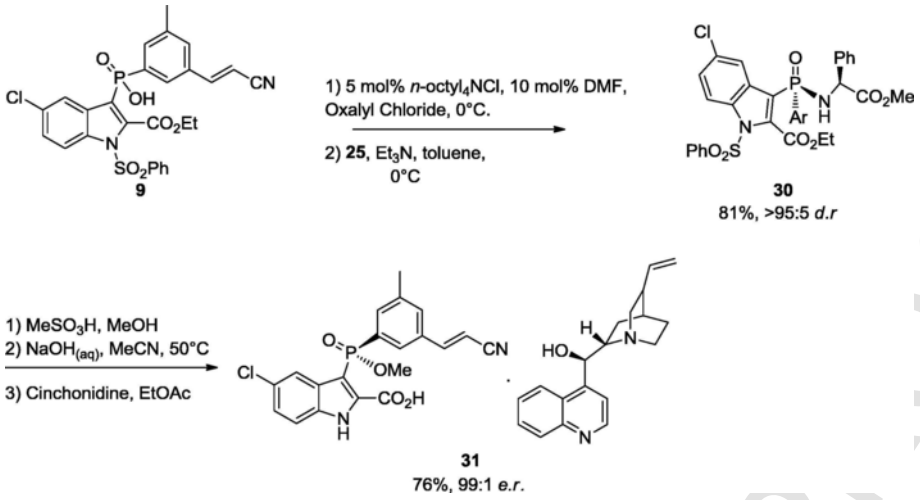
[a] Reagents and conditions: amine (1.5 eq.), base (1.5 eq.), additive (3 eq.), THF, −20 °C.

[b] The ratio of diastereomers was determined by HPLC detecting at 220 nm after 18 h (see ESI for details).

[c] The ratio of diastereomers in the parent compound was determined after 1 h not at full reaction conversion.

[d] None of the desired product observed to determine *d.r.*

[e] Reaction performed in toluene.



Scheme 4. Summary of optimized DKR process, hydrolysis and Cinchonidine salt formation ran on 10 g scale.

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