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An efficient synthesis of highly functionalized chiral lactams

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ABSTRACT

A new method was developed to synthesize highly functionalized lactams via a one pot reductive amination/lactam formation reaction. This methodology is amenable for parallel synthesis and was used to prepare a large number of lactam analogs in a library format with good ee (de) retention.

Introduction

The androgen receptor (AR) is a member of the nuclear hormone receptor superfamily and plays an integral role in primary and secondary male sexual development.[1] This receptor is critical in the development and progression of prostate pathologies, such as prostatic hyperplasia and prostate cancer; thus the modulation of the AR function has been of particular importance in the treatment of these diseases.[2]

While pursuing an orally active Androgen Receptor (AR) antagonist, we became interested in a series of compounds with a general structure shown in the Figure 1.

This series of compounds was prepared previously for a topical application[3] by opening (*R*)-pantolactone with benzylic amines and forming the lactam ring by displacement of the mesylate, which was formed in situ (Scheme 1).

Other syntheses of this class of molecule employed one of two methods: either alkylation of the lactam after ether bond formation[4] or chiral reduction via transfer hydrogenation of an appropriately substituted α-ketopantolactam followed by a reaction to form the ether linkage.[5] The transfer hydrogenation method has the advantage of preserving the chiral center, while alkylation of the (*R*)-lactam core usually resulted in significant racemization (Scheme 2).

(*R*)- and (*S*)-Pantolactones are commonly used chiral auxiliaries.[6–9] Racemic pantolactone has also been used to synthesize racemic pantolactams under high temperature and pressure,[10,11] but further chiral separation via chromatographic, enzymatic, or chemical methods was required to obtain enantiopure material.[12] In order to avoid costly and time consuming chiral separations, we developed a synthesis of pantolactams which would preserve

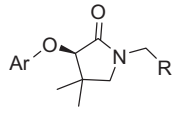

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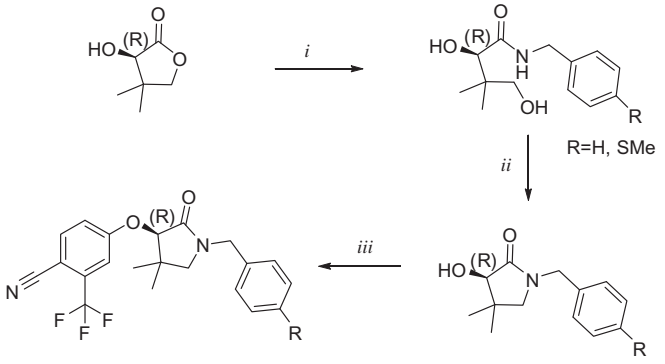
Figure 1. Lactam series.



Scheme 1. Synthesis of lactams by ring opening reaction of (*R*)-pantolactone with benzylic amines. Reagents and conditions: (i) Benzylamine, toluene, 70 °C (R = H, 87%; R = SMe, 95%); (ii) MsCl, Et_3N, NaHMDS (R = H, 61%; R = SMe, 76%); (iii) 4-fluoro2-(trifluoromethyl)benzonitrile, K_3PO_4, NaOH (R = H, 72%; R = SMe, 94%).

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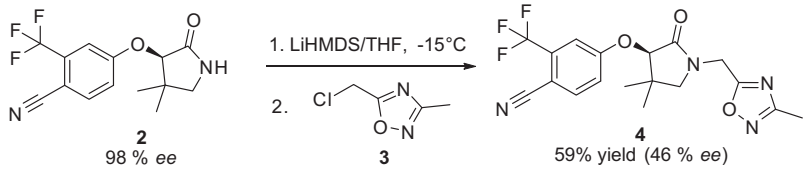
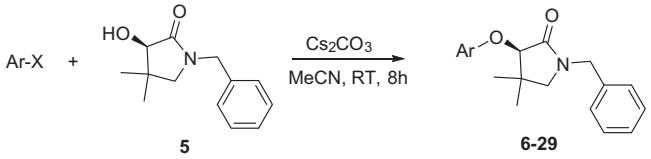
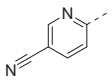
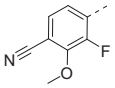
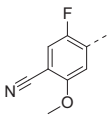
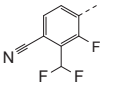
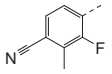
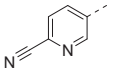
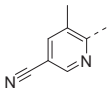
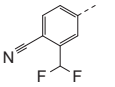
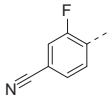
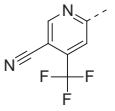
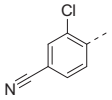
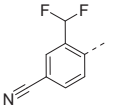
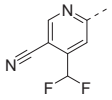
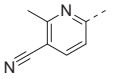
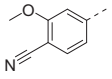
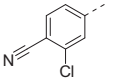
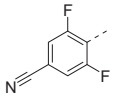
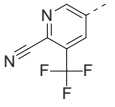
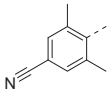
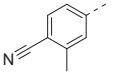
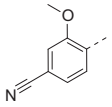
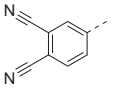
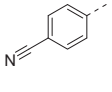
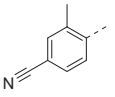


Scheme 2. Lactam alkylation reactions.

Table 1
S_NAr reaction of benzyl pantolactam with aryl halides: Chiral HPLC results

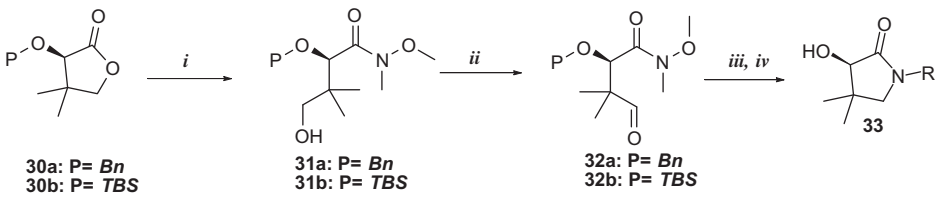


No.	Ar	% ee	No.	Ar	% ee	No.	Ar	% ee	No	Ar	% ee
6		>99	**12**		98	**18**		97	**24**		94
7		>99	**13**		98	**19**		96	**25**		>93
8		98	**14**		97	**20**		96	**26**		93
9		98	**15**		97	**21**		96	**27**		90
10		98	**16**		97	**22**		96	**28**		87
11		98	**17**		97	**23**		96	**29**		83

the chirality of the readily available and inexpensive chiral starting material (*R*)-pantolactone while allowing systematic parallel optimization of the left and right moieties of the molecule.

The first step for this process was to determine whether the S_NAr reaction that forms the ether linkage would cause any racemization of the chiral center. For this purpose chiral alcohol **5**, obtained in 98% ee from the resolution of the racemic material using chiral SFC, was treated with 19 aryl halides and 2 equiv of cesium carbonate in acetonitrile at room temperature for 8 h. Most reactions gave complete conversion by LCMS, and the isolated yields ranged from 4–80% after HPLC purification. The purified compounds were also analyzed by chiral HPLC[13] (Table 1). These results showed that the S_NAr reaction occurred with good retention of stereochemical integrity. Moreover, the ee values correlated with the reactivity of the aryl halide – reactions that gave low conversion and low yield (e.g., example **28**, 4% isolated yield, 87% ee) gave lower ee values when compared to reactions that gave complete conversion and good yields (e.g., example **20**, 77% isolated yield, 96% ee).

Once we confirmed that the ether bond could be formed with good retention of stereochemistry; we explored several methods



Scheme 3. Synthesis of templates. Reagents and conditions: (i) *N,O*-dimethylhydroxylamine (HCl), *i*-propylmagnesium chloride, THF 0 °C, phosphate buffer pH = 7; (ii) DMSO, $(COCl)_2$, DCM, −78 °C; (iii) R-NH_2, $NaBH(OAc)_3$, DCM; (iv) P = Bn; Pd/C; P = TBS; TBAF or $Et_3N{\cdot}HF$.