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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

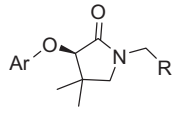
The androgen receptor (AR) is a member of the nuclear hormone receptor superfamily and plays an integral role in primary and secondary male sexual development.[1] This receptor is critical in the development and progression of prostate pathologies, such as prostatic hyperplasia and prostate cancer; thus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

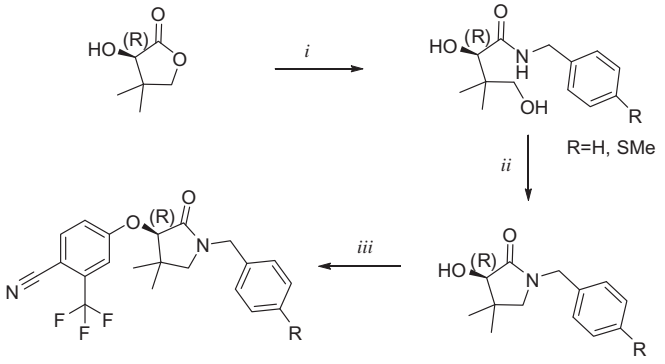
Other syntheses of this class of molecule employed one of two methods: either alkylation of the lactam after ether bond formation[4] or chiral reduction via transfer hydrogenation of an appropriately substituted α-ketopantolactam followed by a reaction to form the ether linkage.[5] The transfer hydrogenation 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



1

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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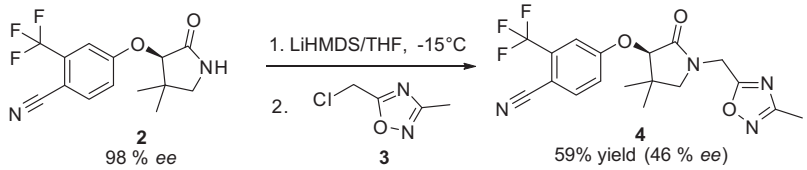
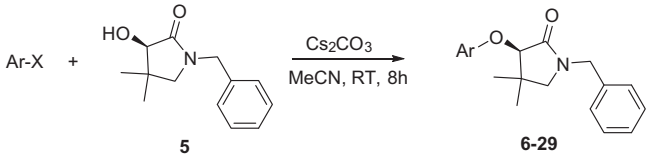
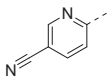
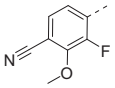
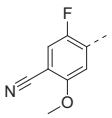
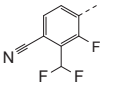
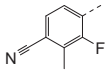
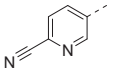
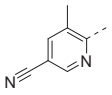
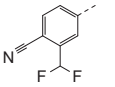
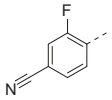
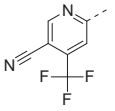
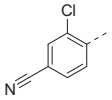
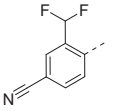
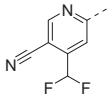
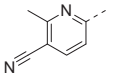
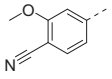
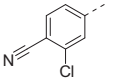
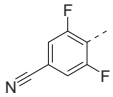
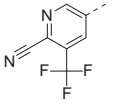
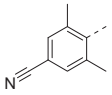
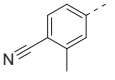
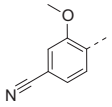
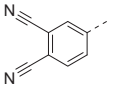
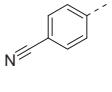
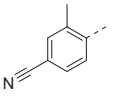


Scheme 2. Lactam alkylation reactions.

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

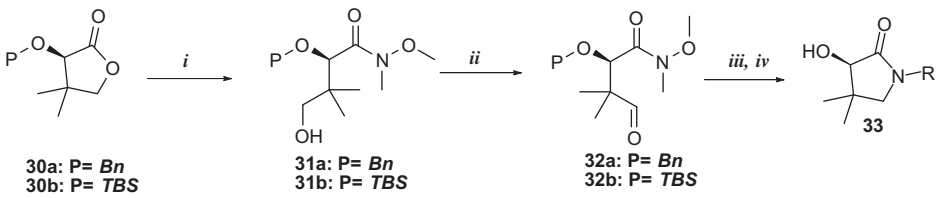


No.	Ar	% ee	No.	Ar	% ee	No.	Ar	% ee	No	Ar	% ee
6		>99	**12**		98	**18**		97	**24**		94
7		>99	**13**		98	**19**		96	**25**		>93
8		98	**14**		97	**20**		96	**26**		93
9		98	**15**		97	**21**		96	**27**		90
10		98	**16**		97	**22**		96	**28**		87
11		98	**17**		97	**23**		96	**29**		83

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.

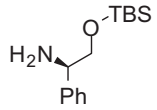
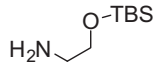
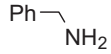
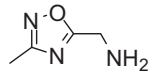
The first step for this process was to determine whether the S_NAr reaction that forms the ether linkage would cause any racemization of the chiral center. For this purpose chiral alcohol **5**, obtained in 98% ee from the resolution of the racemic material using chiral SFC, was treated with 19 aryl 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 $Et_3N{\cdot}HF$.

Table 2
Comparison between reductive amination methods employed for the synthesis of the templates **33**

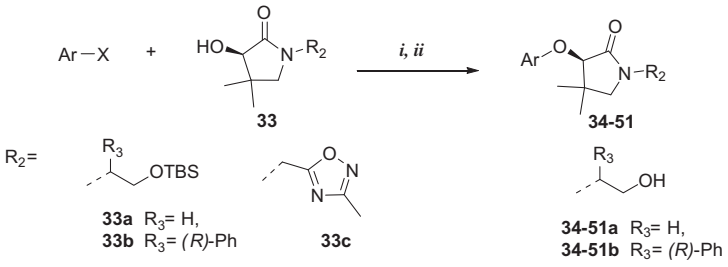
Entry	Amine	$NaBH_4$[c]	$NABH(OAc)_3$[c]	pK_a[d]
1		46[a]	56[a]	8.61
2		52[a]	99[a]	8.78
3		51[a]	NA	9.40
4		40[a]	65[b]	6.34

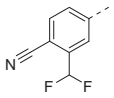
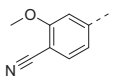
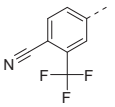
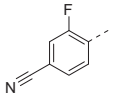
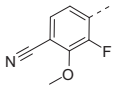
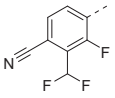
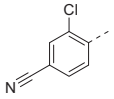
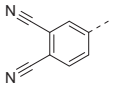
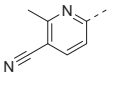
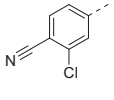
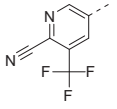
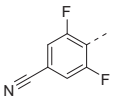
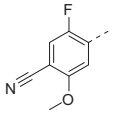
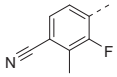
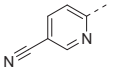
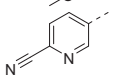
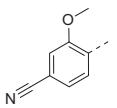
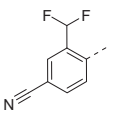
[a] *O*-Benzyl protected aldehyde was used.
[b] *O*-TBS protected aldehyde was used.
[c] Isolated yields (%).
[d] The basicity (pK_a) of the amines was estimated using ACDlab v9.3 software.

to prepare alkylated pantolactams **33**, which are analogs of compound **5**.

The best results were obtained with the procedure shown in Scheme 3. A benzyl or TBS protected pantolactone[14] **30** was treated with *N*,*O*-dimethylhydroxylamine hydrochloride and isopropylmagnesium chloride at 0 °C,[15] affording quantitative yields of alcohols **31a** or **31b**. It is important to note that this step requires a work-up with phosphate buffer pH 7, and it is necessary to immediately use this unstable intermediate after isolation. Alcohols **31a** and **31b** cyclize to the starting lactones upon standing or under alternative work-up conditions such as aqueous ammonium chloride. Swern oxidation[16] also proceeds in good yield. The resulting aldehydes **32a** and **32b** are very stable and can be stored for prolonged periods at 0 °C.[17] One-pot reductive amination/cyclization of **32a** and **32b** was initially run using sodium borohydride in methanol. However, these conditions gave incomplete conversion and competing reduction of the starting aldehyde was also observed. The use of sodium triacetoxyborohydride in dichloromethane or acetonitrile[18] greatly improved the yield of the desired lactams (**33**). Table 2 shows a comparison between these methods for four sample amines. Yields varied depending on the nature of the amine used—the more basic and less hindered amines (entry 2, calcd pK_a = 8.78) gave better conversions, while branched (entry 1, calcd pK_a = 8.61) and less basic amines (entry 4, calcd pK_a = 6.34) gave lower yields; presumably the steric bulk and lower reactivity contributed to the lower yields for the latter. In most reactions the lactam formed spontaneously during the reductive amination, but in some cases cyclization to the lactam did not occur until the aqueous work-up (entry 1). To obtain the desired alcohol templates **33**, the protecting groups were cleaved by hydrogenolysis (P = Bn) or TBAF (P = TBS).

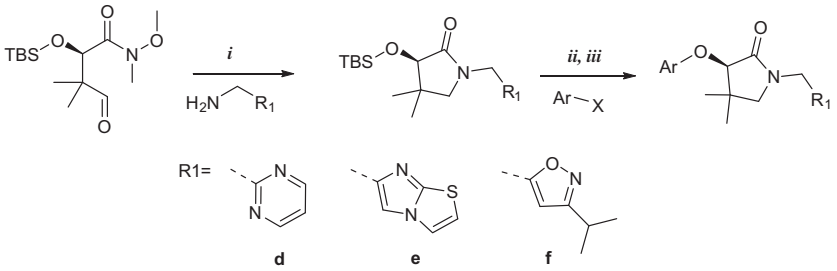
Table 3
S_NAr reactions of chiral alcohol templates chiral HPLC results

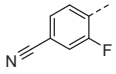
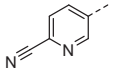
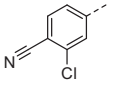
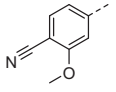
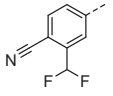
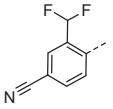
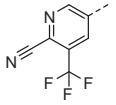
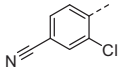
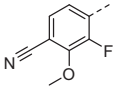


No.	Ar	% ee	No.	Ar	% ee	No.	Ar	% ee
34		a: 65% ee b: 99% de c: 85% ee	**40**		a: 52% ee c: 65% ee	**46**		b: 85% ee c: 57% ee
35		a: 52% ee b: 25% ee	**41**		a: 64% ee c: 66% ee	**47**		c: 94% ee
36		b: 91% de c: 60% ee	**42**		c: Racemic	**48**		a: 76% de b: 89% de c: 94% ee
37		a: 63% ee b: 97% de c: 53% ee	**43**		c: 27% ee	**49**		a: 56% ee c: 96% ee
38		a: 48% ee b: 93% de c: 50% ee	**44**		b: 95% ee c: 31% ee	**50**		a: 99% ee c: 99% ee
39		a: 64% ee b: 99% de c: 84% ee	**45**		a: 92% ee c: 64% ee	**51**		a: 67% ee b: 99% ee c: 93% ee

Reagents and conditions: (i) Cs_2CO_3, MeCN, rt, 8 h; (ii) for a and b; TBAF, THF/water, rt.

Table 4
Tandem reductive amination/cyclization-S_NAr reaction library



No.	Ar	% ee	No.	Ar	% ee	No.	Ar	% ee
52		d: >99% ee f: 95% ee	**55**		e: 99% ee f: 58% ee	**58**		e: 91% ee f: 73% ee
53		d: >99% ee	**56**		e: 94% ee f: 78% ee	**59**		f: 63% ee
54		e: 99% ee f: 84% ee	**57**		e: 94% ee f: 79% ee	**60**		f: 62% ee

Reagents and conditions: (i) $NaBH(OAc)_3$, DCM, rt; (ii) TBAF, THF/water, rt; (iii) Cs_2CO_3, MeCN, rt, 8 h.

The templates **33a–c** were used for parallel synthesis involving S_NAr reactions with aryl fluorides or bromides. For the templates bearing an *O*-TBS moiety on the right-hand side of the molecule, the deprotection step was done using tetrabutyl ammonium fluoride. The general reaction scheme and results for the chiral HPLC analysis for these compounds are shown in the Table 3.

For the next round of synthesis; we were interested in exploring both the left and right portions of the molecule simultaneously in a full matrix fashion to allow us to explore both the best combinations and to address the question of additivity for this series. For this purpose, a tandem reductive amination/cyclization, S_NAr reaction procedure was developed using the aryl halides and amines to give products with the best calculated properties such as MW, *c* log *D*, PSA, and docking scores. Table 4 summarizes the results obtained from this library. From this data we observed the general trend seen previously for the stepwise reactions regarding the reactivity of the aryl halide; furthermore, the nature of the tail piece also had an effect on the erosion of the enantiomeric excess at the chiral center. The products containing the right-hand pieces **d** and **e** showed better ee values, whereas the moiety **f** -an oxygen bearing heterocycle- showed decreased enantiopurity at the chiral center, presumably due to the increased acidity of the lactam α-proton.

In conclusion, a method was developed to prepare alkoxy chiral lactams under mild conditions starting from cheap, commercially available (*R*)-pantolactone. In most cases the products were obtained with general good ee (de) retention. The ee values for the products were affected by the reactivity of the aryl halides and the nature of the right-hand moiety. This method is amenable to parallel synthesis and can be used to prepare diverse and highly substituted chiral lactams with high enantiopurity that would not be accessible by other methods, such as direct alkylation of the lactam ring.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.07.021.

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13. HPLC analysis was carried out using a 150 × 4.6 mm I-CH ChiralPak® column at 40 °C. Mobile phase A (MPA) was neat heptane while mobile phase B (MPB) was a 1:1 methanol: ethanol mix. The gradient began at a 95:5 ratio of MPA:MPB and was held at this level for 5 min before being increased to 30% over 20 min at a flow rate of 2.5 mL/min. The method run-time was 30-min with a 5-min re-equilibration. UV response at 254 nm was used for quantization. 5 μL injections were made directly from diluted ethanol solutions of approximately 1 mg/mL.
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