

## Approach Towards the Total Synthesis of Cyclopeptide Alkaloids

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**Abstract:** Macrocyclization via formation of aryl-alkyl ether bond was a key step in a model synthesis of 14-membered cyclopeptide alkaloids. A new chemoenzymatic synthesis of chiral 2-amino-1-arylethanol was developed in the course of this study  
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Cyclopeptide alkaloids are a family of *para* or *meta* cyclophanes with a polypeptidic tether.<sup>1</sup> The widespread occurrence of these 13-, 14- and 15-membered macrocyclic molecules have made them an important class of natural products. Since the first structural determination of pandamine **1** by Goutarel and Païs in 1966,<sup>2</sup> over 200 compounds of this family have been now identified. Characteristic to these natural products is the presence of 1) an aryl alkyl ether bond in 13- and 14-membered macrocycles; 2) *erythro*  $\beta$ -hydroxy- $\alpha$ -amino acid, most frequently  $\beta$ -hydroxyproline,  $\beta$ -hydroxyleucine and  $\beta$ -hydroxyphenylalanine, and 3) a hydroxyphenethylamine, its oxidized or most commonly dehydrated form as in zizyphine-A (**2**). Although a broad spectrum of biological activities has been ascribed to certain members, their limited availability from natural sources has hampered extensive pharmacological investigations and consequently, their biological profile has not yet been well defined.<sup>1</sup>

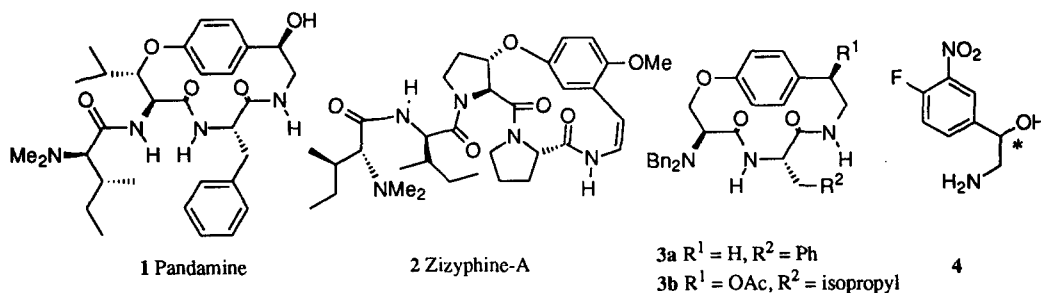
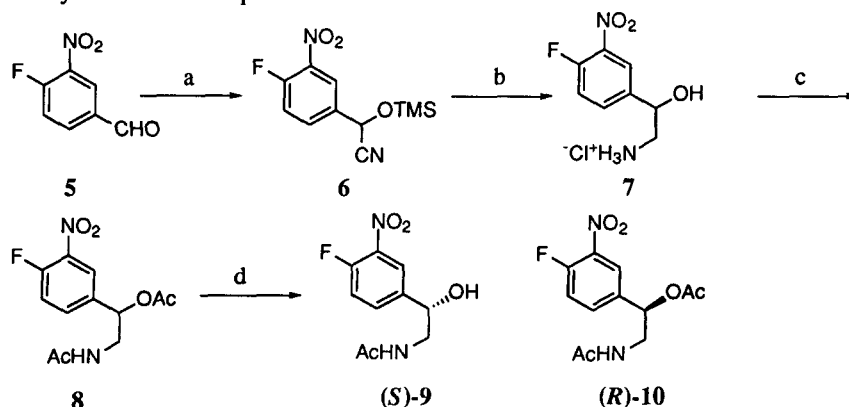


Figure 1

Their scarcity as well as their unique structural features have made cyclopeptide alkaloids attractive synthetic targets. Different strategies have been envisaged by a number of groups and total syntheses of several natural products<sup>3</sup> have been achieved by way of macrolactamization techniques developed by Rapoport,<sup>4</sup> Schmidt,<sup>5</sup> Joullie<sup>6</sup> et al. Alternatively, Lawton's group<sup>7</sup> attempted biomimetic intramolecular Michael addition as a key ring forming step and Lipshutz developed an intramolecular amide alkylation<sup>8</sup> using oxazolophanes as masked peptide synthon.

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As a logical extension of our work on the synthesis of macrocycles containing an endo aryl-aryl ether bond using intramolecular  $S_NAr$  methodology,<sup>9,10</sup> we have very recently reported a new macrocyclization process in which aryl-alkyl ether bond was formed with concomitant ring formation.<sup>11</sup> To further illustrate the potential of such strategy, we describe herein a concise synthesis of cyclophane **3b** (Figure 1) wherein an optically pure hydroxyphenethylamine was incorporated.

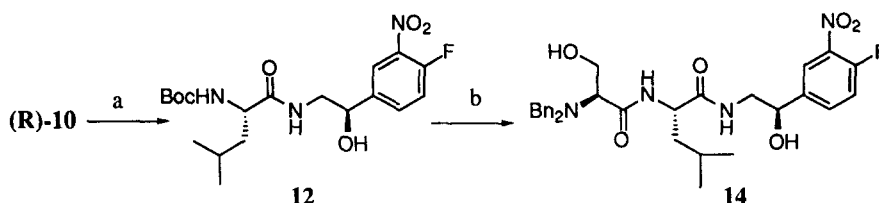


Reagents and Conditions: a) TMSCN, ZnI<sub>2</sub>; b) BH<sub>3</sub>-THF, reflux, 90%; then MeOH-HCl; c) Ac<sub>2</sub>O, Et<sub>3</sub>N, DMAP, 85%; d) HLE, phosphate buffer pH = 7.5 and acetone, isolated yield: *(S)*-**9**, 46% and *(R)*-**10**, 45%

Scheme 1

An efficient synthesis of optically pure 2-amino-1-(4-fluoro-3'-nitro) ethanol was prerequisite for pursuing the synthesis of **3b** and other natural products. One of the obvious routes to enantiomerically pure amino alcohol of type **4** is the reduction of the corresponding chiral cyanohydrins which are available by way of both chemical<sup>12</sup> and enzymatic<sup>13</sup> procedures. However, literature survey revealed that electron deficient arylaldehydes (e.g., nitrobenzaldehyde) were generally poor substrates in enantioselective synthesis of cyanohydrins.<sup>14</sup> Our interest in the chemoenzymatic synthesis of chiral building blocks<sup>15</sup> prompted us to examine an alternative way, i.e., enzymatic resolution of racemic amino alcohol derivative **8** as shown in Scheme 1. Lewis acid (ZnI<sub>2</sub>) catalyzed addition of TMSCN<sup>16</sup> to 4-fluoro-3-nitrobenzaldehyde gave cyanohydrin **6** which was chemoselectively reduced to amino alcohol, isolated as the hydrochloride salt **7** in 90% overall yield. Acylation under standard conditions gave then product **8**. While several reports dealing with the enzymatic resolution of 2-amino-2-alkylethanol<sup>17</sup> have appeared, research on 2-amino-1-arylethanol was relatively rare.<sup>18</sup> After much experimentation varying the enzyme, the solvent and the acyl moiety,<sup>19</sup> the optimal conditions found for the resolution of **8** were HLE in mixed solvent (phosphate buffer, pH = 7.5 and acetone) at 27°C. The *S*-enantiomer was selectively hydrolyzed and both *(S)*-**9** and unreacted *(R)*-**10** were isolated in 45% and 46% yields, respectively. The enantiomeric purity of compounds **9** and **10** (*ee* > 90%) was determined by derivatization with *(S)*-2-acetoxy propionyl chloride while their absolute configuration was established by Mosher's method.<sup>19</sup>

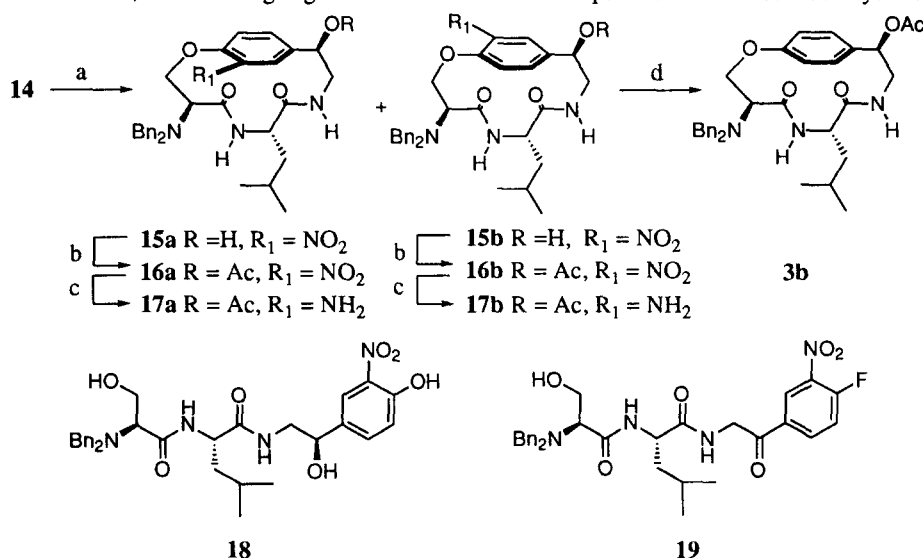
With chiral *(R)*-**10** in hands, the cyclization precursor was synthesized as shown in Scheme 2. Deacetylation of *(R)*-**10** under acidic conditions gave the corresponding amino alcohol which was coupled with L-*N*-Boc-Leu (**11**) to give dipeptide **12** in 92% yield. Mild acidic deprotection (HCl-MeCN) of *N*-Boc function followed by reaction with L-*N,N*-dibenzyl Ser (**13**) gave the linear precursor **14** in 80% overall yield. We observed that protection of hydroxyl functions was redundant in these two coupling steps.



Reagents and Conditions: a) i: 6N HCl, ii: L-N-Boc Leu (11), EDC, HOBt, 92%; b) i) HCl-MeCN (15% v/v), ii) EDC, HOBt, L-N,N-dibenzyl Ser (13), 80%

Scheme 2

Treatment of a DMF solution of **14** (0.01M) with TBAF in the presence of molecular sieves (3Å) at room temperature gave two separable cyclic monomers **15a** (30%) and **15b** (35%) whose structures were assigned as two atropisomers from spectroscopic studies and were confirmed by subsequent chemical transformation (*vide infra*). A striking feature of this cyclization is the absence of  $\beta$ -elimination process of cyclic product which was the major concern at the outset of this work.<sup>20</sup> We proposed that the "protecting group tuning effect"<sup>21</sup> was operating in this case and that the protection of terminal nitrogen as *N,N*-dibenzyl amino group was essential for the stability of cyclic products for it renders, both kinetically and thermodynamically, the  $\alpha$ -proton of serine less prone to be abstracted. From the cyclization mixture, a variable amount of hydroxylated product **18** was also isolated which might result from the intermolecular  $S_NAr$  reaction between **14** and adventitious  $H_2O$  in the reaction medium. THF was also a suitable solvent though the reaction time was significantly prolonged (4 h in DMF vs 4 days in THF). With the idea to further activate the fluoronitroaromatic rings towards the nucleophilic attacks, keto derivative **19** was prepared. However, when this compound was submitted to the above mentioned cyclization conditions, an interesting degradation<sup>22</sup> occurred at the expense of the desired macrocyclization.



Reagents and Conditions: a) TBAF, DMF, molecular sieves 3Å, 65%; b)  $Ac_2O$ ,  $Et_3N$ , DMAP, 85% c)  $NaBH_4$ , elemental sulfur; d)  $^tBuONO$ ,  $BF_3 \cdot OEt_2$ , e) Fe,  $FeSO_4$ , DMF, 65%.

Scheme 3

Removal of nitro group was straightforward (Scheme 3). Reduction of O-acylated derivatives **16a** and **16b** with sulfurated NaBH<sub>4</sub><sup>23</sup> in THF gave the corresponding amino compounds **17a** and **17b**. Diazotization of **17a** and **17b** under Doyle's condition<sup>24</sup> followed by FeSO<sub>4</sub> mediated reduction of crude diazonium salt<sup>25</sup> gave the same 14-membered *p*-cyclophane **3b** in 65% overall yield.

In conclusion, we have demonstrated that macrocyclization via formation of an aryl-alkyl ether bond is an efficient methodology for the synthesis of strained 14-membered cyclopeptide alkaloids. A new chemoenzymatic synthesis of 2-amino-1-arylethanol was also developed in connection with the present work.

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