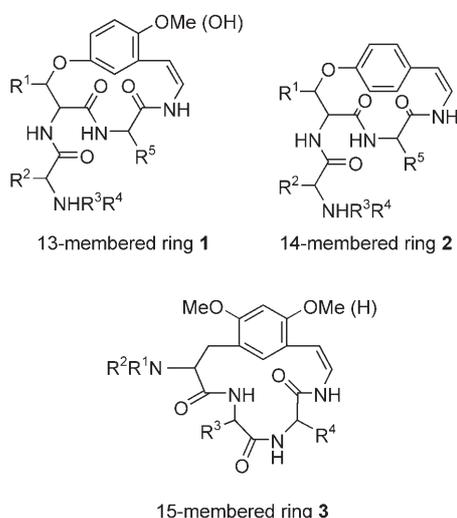


## Total Synthesis of Paliurine F\*\*

Mathieu Toumi, François Couty, and Gwilherm Evano\*

Dedicated to Professor James S. Panek on the occasion of his 50th birthday

Cyclopeptide alkaloids are natural products that have been isolated from the leaves, stem bark, root bark, and seeds of a wide variety of plant species throughout the world. They are distinguished by their structural similarity and possess a 13- (1), 14- (2), or 15-membered (3) cycle containing an aromatic ring. The remainder of the macrocycle consists of a peptide unit that is connected to the aromatic ring in either a 1,4 or 1,3 orientation with enamide and alkyl aryl ether (or methylene) linkages (Scheme 1). To date, over two hundred



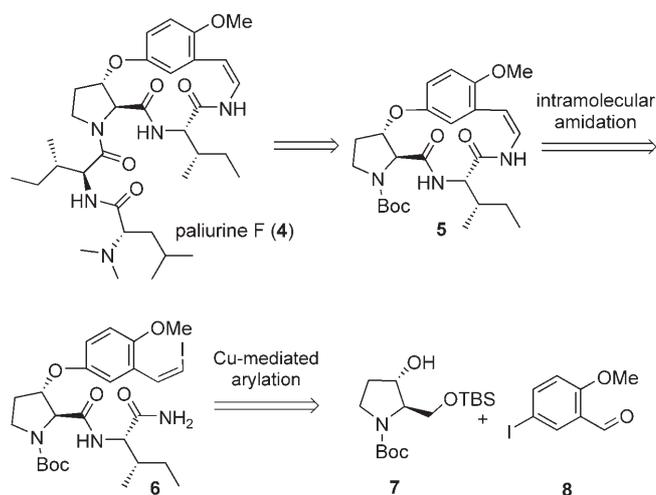
**Scheme 1.** Cyclopeptide alkaloids: 3 subclasses, over 200 members.

structures have been described and these natural products, which have been used historically for the treatment of a variety of ailments, have been shown to have numerous biological activities which include sedative, antibacterial, antifungal, and antiparasitic effects.<sup>[1]</sup>

The interesting topology of these natural products, coupled with their restricted natural availability (0.0002–1%

of dried plants), prompted immediate interest from the synthetic community. Thus, several strategies have been used for the key macrocyclization step. The initial report by Schmidt et al.<sup>[2]</sup> utilized the macrolactamization of a pentafluorophenyl ester, which was later used in total syntheses by the research groups of Joullié<sup>[3]</sup> and Han.<sup>[4]</sup> The synthesis of sanjoinine G1 and the mauritines by Zhu and co-workers incorporated an intramolecular  $S_NAr$  reaction as the macrocyclization protocol.<sup>[5]</sup> Examination of these syntheses, along with the synthetic approaches to these alkaloids,<sup>[6–8]</sup> reveals that the moderately complex chemical structure of these natural products is a challenging target. Primary synthetic challenges that must be overcome are: a) the formation of the alkyl aryl ether, b) the enamide formation, and c) the macrocyclization. Herein, we report our efforts in this field, which led not only to the first total synthesis of the sedative cyclopeptide alkaloid paliurine F (4),<sup>[9,10]</sup> but also to the use of the recently developed copper(I)-mediated coupling reactions for the installation of the key structural elements of paliurine F and for the macrocyclization step.

From a retrosynthetic perspective, we envisioned installation of the peptidic side chain late in the synthesis, thereby permitting construction of paliurine F from the advanced precursor 5 as depicted in Scheme 2. To install the cyclic enamide and simultaneously effect macrocyclization, we decided to employ a challenging intramolecular copper(I)-mediated amidation reaction<sup>[11–13]</sup> using the amido vinyl iodide 6 as the enamide precursor. Further analysis of 6 suggested a disconnection at the aryl ether bond to give the hydroxypyrrolidine 7 and the aromatic fragment 8, which



**Scheme 2.** Retrosynthetic analysis of paliurine F (4). Boc = *tert*-butyloxycarbonyl, TBS = *tert*-butyldimethylsilyl.

[\*] M. Toumi, Prof. F. Couty, Dr. G. Evano  
Institut Lavoisier de Versailles, UMR CNRS 8180  
Université de Versailles Saint-Quentin en Yvelines  
45, avenue des Etats-Unis, 78035 Versailles Cedex (France)  
Fax: (+33) 1-3925-4452  
E-mail: evano@chimie.uvsq.fr

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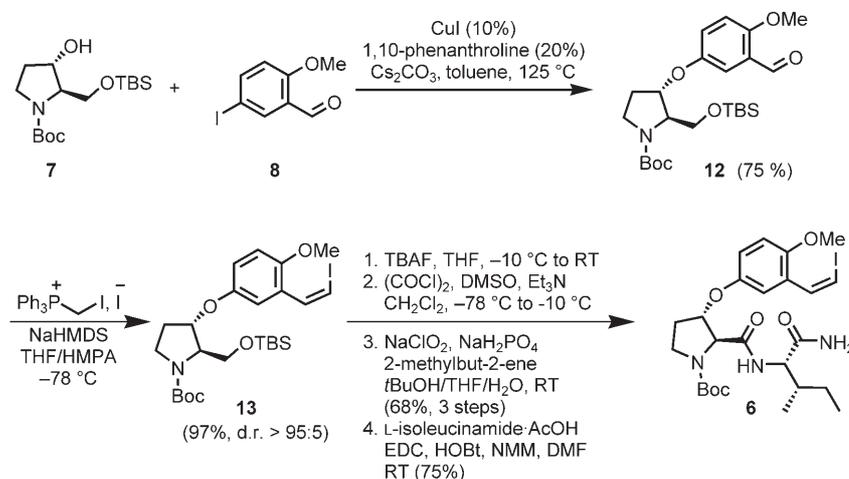
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could be coupled together using a copper-mediated arylation reaction.<sup>[14]</sup>

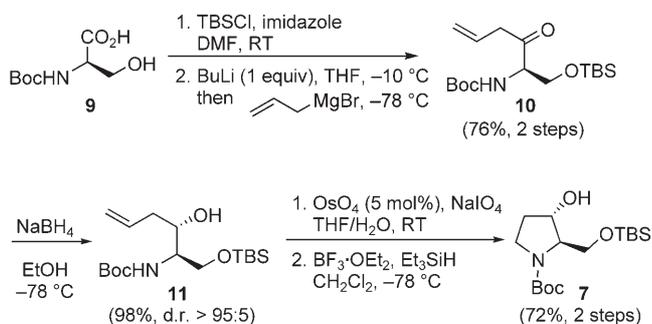
Our synthesis began with the asymmetric preparation of the hydroxypyrrolidinol **7**.<sup>[15]</sup> Our goal was to design a substrate-controlled asymmetric route with a limited number of steps and protecting groups to enable synthesis of multigram quantities of this fragment. Therefore, the commercially available *N*-Boc-*D*-serine **9** was chosen as the starting point of the synthesis (Scheme 3). The treatment of **9** with excess TBSCl in DMF followed by acidic workup allowed for smooth protection of the alcohol. The resulting free carboxylic acid was subjected to a modification of the Tegner reaction reported by Knudsen and Rapoport,<sup>[16]</sup> which involved deprotonation of the acid with one equivalent of butyllithium followed by addition of two equivalents of allylmagnesium bromide. This route afforded the unconjugated ketone **10** in good yield and without any epimerization. Ketone **10** was then used to introduce the second stereo-center of the target molecule. We were delighted to find that simple treatment of **10** with sodium borohydride provided the desired protected amino diol **11** as a single diastereoisomer (through NHBoc-chelation control),<sup>[17]</sup> even though reduction of related substrates is known to mainly proceed with poor to moderate selectivity.<sup>[18]</sup> Formation of the pyrrolidine ring was initiated by oxidative cleavage of the double bond; spontaneous cyclization of the intermediate aminoaldehyde followed by reduction of the resulting protected aminoal using boron trifluoride and triethylsilane ultimately gave the desired hydroxypyrrolidine **7** in 54% overall yield from *N*-Boc-*D*-serine **9** (in five steps with one purification).

We next investigated the Ullmann-type copper-mediated arylation<sup>[14]</sup> between the highly functionalized cyclic alcohol **7** and aryl iodide **8**<sup>[19]</sup> for the assembly of the acyclic fragment **6**. After screening several reaction conditions, it was determined that this coupling was best effected by using a slight modification of the procedure reported by Buchwald and co-workers.<sup>[14a]</sup> This involved using CuI (10 mol %), 1,10-phenanthroline

(20 mol %), and cesium carbonate as a base in toluene at 125 °C and using a slight excess (1.4 equiv) of the iodide **8** (Scheme 4). Under these conditions, pyrrolidinyl aryl ether **12** was obtained in 75% yield. After coupling fragments **7** and **8**, several chemical manipulations were necessary before the macrocyclization procedure. To that end, the (*Z*)-vinyl iodide required for the final macroamidation step was installed stereoselectively using the Stork–Zhao olefination reagent (97%, >95% *de*),<sup>[20]</sup> the TBS ether was deprotected using TBAF in THF, and the resulting primary alcohol was converted into the acid by using a two-step sequence (Swern/buffered NaClO<sub>2</sub> oxidations) in good overall yield. Finally, the second constitutive amino acid of the macrocycle was introduced using an EDC/HOBt-mediated coupling with isoleucinamide. This latter step, which proceeded in 75% yield, allowed us to introduce the amide group necessary for the intramolecular amidation reaction (Scheme 4).

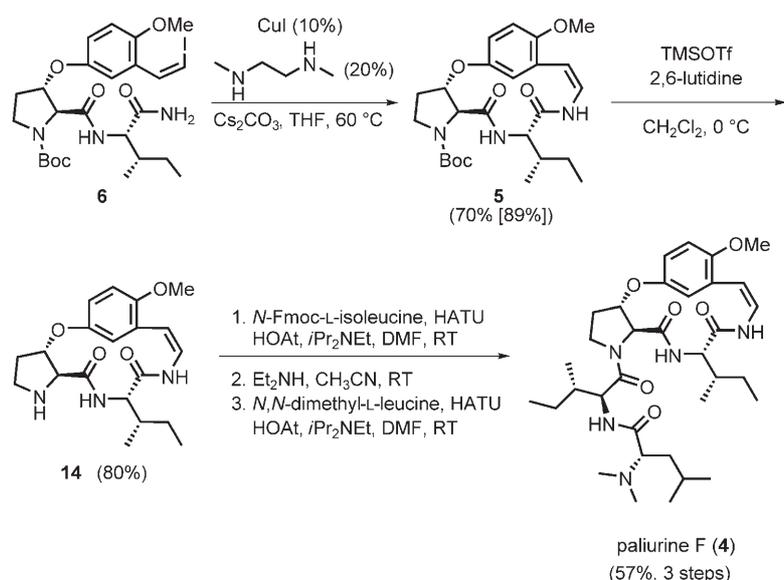


**Scheme 4.** Fragment coupling and assembly of the acyclic skeleton **6**. EDC = 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide, HMDS = 1,1,1,3,3,3-hexamethylsilylazane, HMPA = hexamethyl phosphoramide, HOBt = 1-hydroxy-1*H*-benzotriazole, NMM = *N*-methylmorpholine, TBAF = tetra-*n*-butylammonium fluoride.



**Scheme 3.** Asymmetric synthesis of the hydroxypyrrolidine fragment **7**.

Having the iodoamide **6** in hand, we next explored the crucial macrocyclization step. A brief survey of various catalytic systems reported by the research groups of Porco,<sup>[11]</sup> Buchwald,<sup>[12]</sup> and Ma<sup>[13]</sup> for the amidation of vinyl iodides revealed dramatic differences in reactivity. While initial investigations of the intramolecular amidation using combinations of copper iodide and triphenylphosphine<sup>[11a,21]</sup> or *N,N*-dimethylglycine<sup>[13]</sup> failed to give any cyclization product, [Cu(CH<sub>3</sub>CN)<sub>4</sub>]PF<sub>6</sub>, which was also examined as a copper(I) source, with 3,4,7,8-tetramethyl-1,10-phenanthroline as ligand, afforded the desired product, but only in trace amounts.<sup>[11b]</sup> To our delight, we eventually found that subjecting the acyclic skeleton **6** to copper(I) thiophene-2-carboxylate in *N*-methylpyrrolidine at 90 °C<sup>[11a]</sup> smoothly provided the desired macrocyclic enamide **5** in 60% yield. Switching to the CuI/*N,N*-dimethylethylenediamine catalytic system<sup>[12]</sup> improved the yield slightly, thus providing **5** in 70% yield, along with 20% of recovered starting material. This



**Scheme 5.** Macrocyclization and completion of the synthesis. Fmoc = 9-fluorenylmethoxycarbonyl, HATU = *N*-[(dimethylamino)-1*H*-1,2,3-triazole[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate, HOAt = 7-aza-1-hydroxy-1*H*-benzotriazole, TMS = trimethylsilyl. Yield in square brackets is based on recovered starting material.

procedure allowed a straightforward installation of the cyclic enamide group of the target molecule (Scheme 5).<sup>[22,23]</sup>

Removal of the Boc group was then achieved in good yield using TMSOTf and 2,6-lutidine.<sup>[3b]</sup> Finally, coupling of **14** with *N*-Fmoc-L-isoleucine, followed by removal of the Fmoc group by treatment with diethylamine in acetonitrile, and subsequent coupling with *N,N*-dimethyl-L-leucine gave the desired paliurine F (**4**) in 57% yield over the three final steps (Scheme 5). The physical, spectroscopic, and spectrometric characteristics (<sup>1</sup>H NMR, <sup>13</sup>C NMR, IR, [ $\alpha$ ]<sub>D</sub>, UV, and MS) of synthetic (–)-paliurine F corresponded well to those reported for the natural product.<sup>[9,24]</sup>

In summary, the first total synthesis of paliurine F has been achieved in 16 steps (longest linear sequence) and 6.5% overall yield. Notable features of our synthetic approach include an efficient copper(I)-mediated arylation of a highly substituted alcohol to build the aryl ether bond. Herein we have documented the first example of an intramolecular copper(I)-mediated vinylation to install the 13-membered macrocyclic enamide, thereby further expanding the scope of these underdeveloped useful reactions which allow new bond disconnections in total synthesis. This convergent approach should be easily applicable to the synthesis of 14-membered ring cyclopeptide alkaloids, as well as to the construction of analogues for further biological testing, which will be reported later.

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