Convenient Synthesis of 2,7-Naphthyridine Lophocladines A and B and their Analogues

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Compounds containing a 2,7-naphthyridine scaffold are a small class of bispyridine structures identified in various living organisms (plants, sponges, tunicates, bryozoans). These natural products usually possess variant biological activities, which make them attractive lead compounds for further drug discovery. For example, 3-acetyl-2,7-naphthyridine **1**, isolated from *Valeriana officinalis*, has sedative and tranquillizing activity.[1] Polycyclic alkaloids, sampangine **2**[2] and ascididemine **3**,[3] obtained from *Cleistopholis patens* and *tunicate Didemnum sp.*, respectively, were also reported with high antimicrobial and anticancer activities (Figure 1). More recently, Gross and co-workers[4] reported the isolation of two new bicyclic naphthyridine alkaloids, naphthyridone Lophocladine A (**4**) and aminonaphthyridine Lophocladine B (**5**) from the red alga Lophocladia sp. (Figure 1). In preliminary biological assays, Lophocladine A showed antagonistic activity against δ-opioid receptors, whereas Lophocladine B exhibited cytotoxic activities against breast cancer and lung tumor cell lines.[4]

As part of our drug discovery program toward identification of novel opioid receptor–ligands[5] as potential treatments of drug abuse, we became interested in a convenient synthesis and structure modification of natural alkaloids **4** and **5** and their C-4 substituted analogs, due to the novel structural scaffold-2,7-naphthyridine core.

Compared to the large number of references dedicating to the synthesis of 1,5-, 1,6-, 1,7-, and 2,6-naphthyridines,[6] very limited methods have been reported for the construction of the 2,7-naphthyridine skeleton. Gabriel and others[7] have reported several syntheses of 2,7-naphthyridine analogs, but these methods suffered from low yields, limited starting materials, harsh reaction conditions, and, most importantly, the unavailability to incorporate a C-4 phenyl group in the 2,7-naphthyridine core. In 1996, Couture[8] reported a new synthetic route to *N*-substituted analogs of **4** (Scheme 1, path a) via a Wittig condensation of ketone **7** and phosphinylmethylamine **8**. This was the first synthesis of 4-aryl substituted 2,7-naphthyridine analogs, but this method was also limited by the difficulty in the preparation of the precursors **7** and **8**. In the progress of our synthetic effort, Lotter[9] very recently reported the first total synthesis of 2,7-naphthyridines **4** and **5** by cyclization of enamine **9**, which in turn was made from 4-benzyl-3-cyanopyridine **10** in moderate yield (Scheme 1, path b). Although this represented the first total synthesis of Lophocladine A (**4**) and aminonaphthyridine Lophocladine B (**5**), this method also suffered from the inconvenience in generating a library of C-4 substituted 2,7-naphthyridine analogs.

Our synthetic work was focused on developing a facile strategy to construct the 2,7-naphthyridine library with a ready availability to introduce the variant C-4 substituent. In this regard, we envisioned that a cleavage of naphthyridine **4** by path c (Scheme 1) would lead to a precursor **11**, which can be prepared from nicotinic acid **12** and various *N*-aroylmethyl-*N*-benzylamines **13**. However, after several trials on the cyclization of amide **11** (X = H) using *n*-BuLi, *s*-BuLi, or LDA as the lithiation agent,[10] no cyclization product was observed, except the complete recovery of the starting material **11**. An alternative lithiation method was also attempted by first iodination at the C-4 position of the pyridine ring amide **11** (X = H → I) followed by a halide–metal exchange reaction with *s*-BuLi or LDA.[11] Unfortunately, the following cyclization still did not occur.

Our second effort was started by using a similar procedure reported by Barbu[7j] in 2000, where a 4-nonsubstituted 3-acyl-2,7-naphthyridine was prepared. Treatment of ethyl acetoacetate **14** and cyanoacetamide **15**, followed by hydrolysis, chlorination, and reduction, yielded 4-methyl-3-cyanopyridine **16** with an overall yield of 25% (4 steps) (Scheme 2).[12,13] Reaction of compound **16** with DMF acetal in refluxing DMF resulted in a clean transformation to enamine **17**.[7f,14] The crude enamine **17** was then converted to 2,7-naphthyridin-1-one **18**[14] in 78% yield by treatment with glacial HOAc/H_2SO_4 or to **19**[7e] by heating with NH_4OAc. Bromination[7e,f,15] or iodination of **18** or **19** with Br_2 in glacial HOAc or with I_2/NaOH yielded a sole product which was characterized to be the C-4 brominated/iodinated 2,7-naphthyridines **20a**,**b** or **21a**,**b**. The high regioselectivity of such bromination/iodination can be rationalized by the higher electronegativity of the 1-oxopyridine ring (compound **18**) and the 1-aminopyridine ring (compound **19**) over the unsubstituted pyridine ring in the 2,7-naphthyridine core.

With 4-bromo/iodo-2,7-naphthyridines **20** and **21** as key building blocks, a number of coupling/condensation reactions were conducted. First, a Suzuki coupling[16] of bromide **20a** with phenylboronic acid under the catalytic system of $Pd(PPh_3)_4/Na_2CO_3$ yielded the target Lophocladine A (**4**) in 45% yield (Scheme 3). The spectroscopic data of the synthetic compound **4** was in full accordance with the data described for the alkaloid in the original reference[4] and with the data reported by Lotter.[9] Using same conditions, a number of 4-aryl substituted 2,7-naphthyridin-1-ones (**22a**–**i**) were prepared from variant arylboronic acids without any protection of the amide moiety. In some cases, 4-iodo 2,7-

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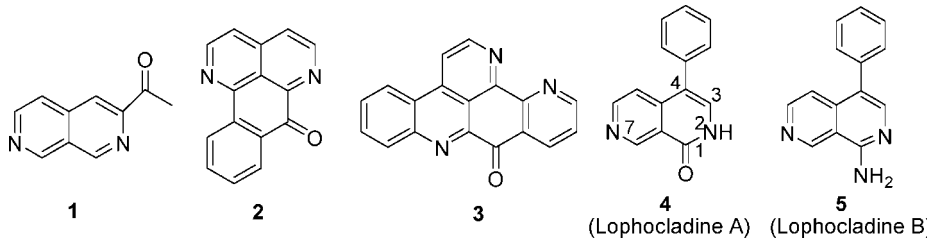
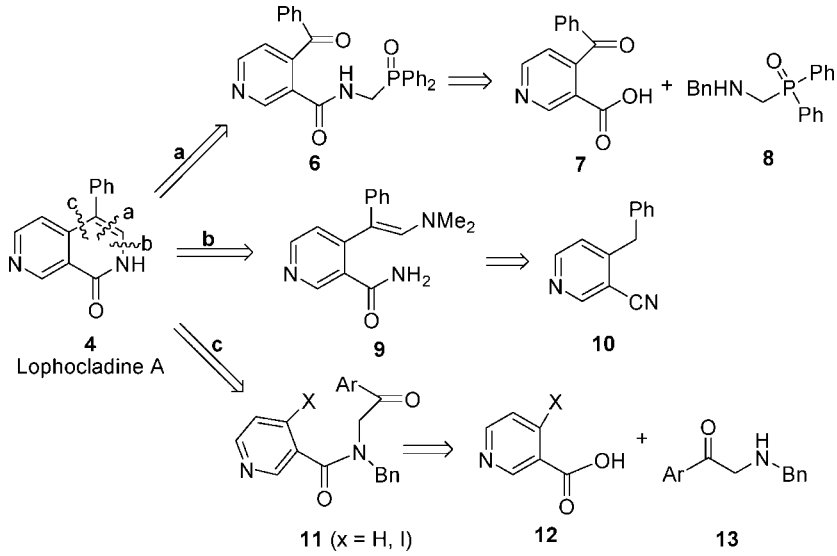
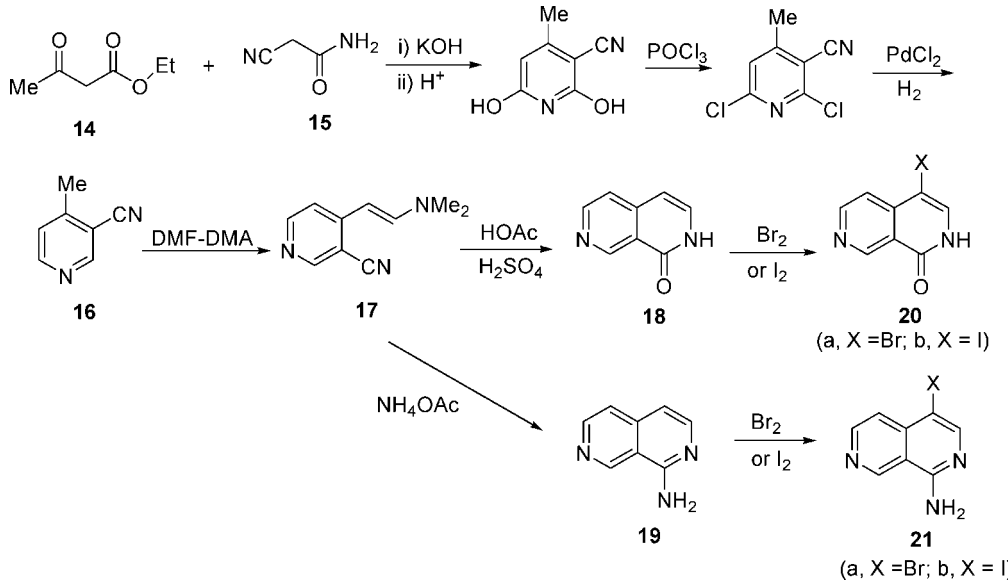


Figure 1. Natural 2,7-naphthyridine alkaloids.

Scheme 1. Retrosynthetic Analysis of Naphthyridine **4** (Paths a, b, and c)

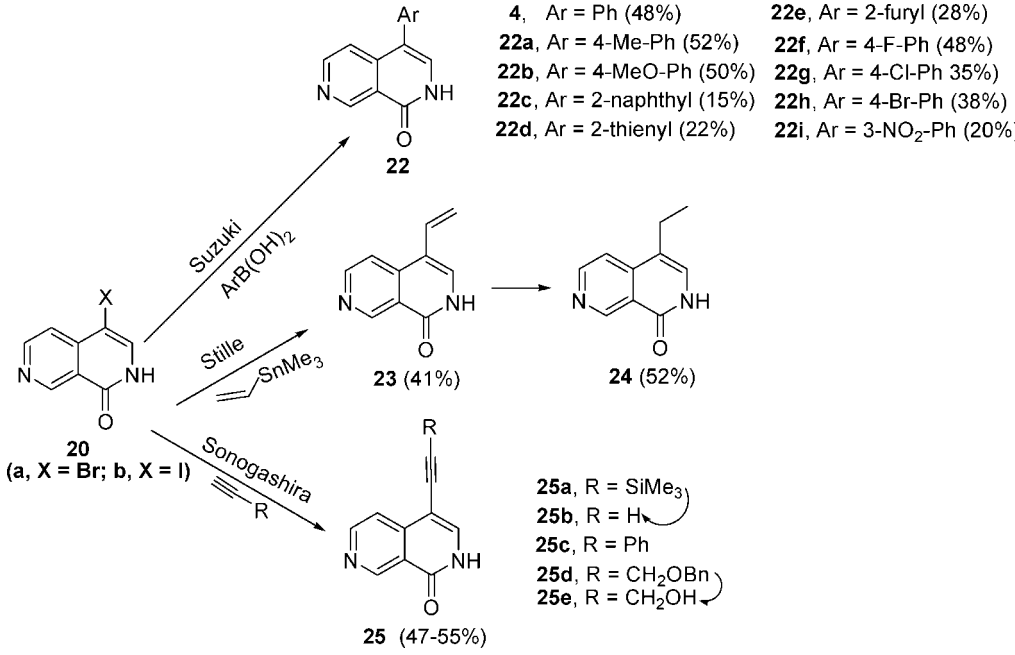


Scheme 2. Preparation of 4-Bromo/Iodo-naphthyridines **20** and **21**



naphthyridin-1-one **20b** gave slightly higher yield than bromide **20a**. Arylboronic acid with an electron-donating substituent (**22a**,**b**) generally gave higher yield (~50%) than the arylboronic acid with an electron-withdrawing substituent (**22f–i**; 20–48%). However, arylboronic acids with relatively larger size (**22c–e**) gave poor yields (15–28%), indicative of the fact that the steric effect plays a role in this reaction. 4-Vinyl-2,7-naphthyridin-1-one **23** was prepared by a Stille coupling[17] of iodide **20b** and tributylvinylstannane under the catalytic conditions[18] of CuI/Pd(PPh_3)$_4$ in 41% yield (Scheme 3). Further hydrogenation of compound **23** with Pd/C under normal pressure led to 4-ethyl analog **24** in 52% yield. Sonogashira reaction[19] of iodide **20b** with an appropriate substituted acetylene yielded 4-trimethylsilylacetylenyl- (**25a**), 4-phenylacetylenyl- (**25c**), and 4-benzyloxymethylacetylenyl- (**25d**) 2,7-naphthyridin-1-ones in moderate yields (47–55%; Scheme 3). Both Stille and Sonogashira reactions gave relatively low yields, partially due to the poor solubility of these products and difficulty in purification. Treatment of compound **25a** with KOH in MeOH gave the desilylated product **25b** in 50% yield. Hydrogenation of compound **25d** with Pd/C yielded the 4-hydroxymethylacety-

Scheme 3. Typical Conditions for the Synthesis of C-4 Substituted Naphthyridin-1-ones[a]



[a] For Suzuki reaction: $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, LiCl, EtOH/toluene, reflux, overnight. For Stille reaction: (vinyl)$SnBu_3$, $Pd(PPh_3)_4$, CuI, DMF, 60 °C, overnight. For Sonogashira reaction: appropriate acetylene, CuI, $Pd(PPh_3)_4$, Et_3N, DMF, rt, overnight.

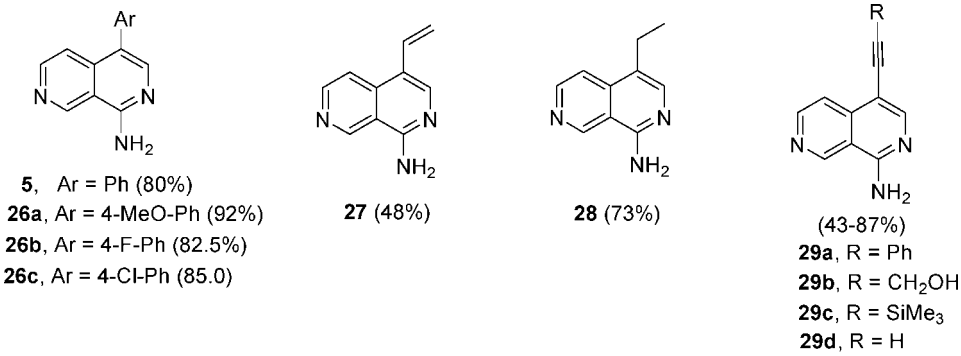


Figure 2. C-4 substituted naphthyridin-1-amines.

lenyl-2,7-naphthyridin-1-one **25e** quantitatively. This compound can also be prepared by treating iodide **20b** with propargyl alcohol in 33% yield directly.

On the basis of the encouraging results above, a similar coupling strategy was also applied to the 4-bromo/iodo-2,7-naphthyridin-1-amine **21a**,**b** (Figure 2). Suzuki coupling of the bromide **21a** with arylboronic acids provided a small class of 4-aryl substituted 2,7-naphthyridin-1-amines (**5** and **26a**–**c**) with high yields (80–92%). The spectroscopic data of the synthetic compound **5** was in full accordance with the data described for the alkaloid in the original reference[4] and with the data reported by Lotter.[9] Stille coupling of iodide **21b** with tributylvinylstannane under the same conditions above yielded the desired **27** (48%), which was smoothly converted to the 4-ethyl analog **28** in 73% yield. Similarly, acetylenyl analogs **29a**–**d** were prepared with iodide **21b** under a similar Sonogashira reaction in moderate–good yields (43–87%). The primary amino group in amine **21** was well-tolerated without additional protection during all the coupling reactions.

In summary, we have developed a convenient and flexible synthetic route to Lophocladines A (**4**) and B (**5**), as well as their C-4 substituted analogs through a regioselective bromination/iodination of 2,7-naphthyridines followed by a Suzuki, Stille, or Sonogashira reaction. Compared to the method reported by Lotter very recently, our method is extremely useful for generation of a 2,7-naphthyridine library (25 members) with variant C-4 substituent, including differently substituted aryl, heteroaryl, as well as vinyl, alkyl, and substituted or nonsubstituted acetylenyl groups. Another advantage of this protocol is that the amido moiety in compound **20** and the amino group in compound **21** were well tolerated without additional protection during all the coupling reactions. Further studies from halides **20** and **21** through other metal-catalyzed coupling reactions as well as bioassays of the synthesized novel 2,7-naphthyridine library are underway.

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Supporting Information Available. Experimental procedures, ^{1}H and ^{13}C NMR, MS, and HRMS, as well as elemental analysis data. This material is available free of charge via the Internet at http://pubs.acs.org.

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