

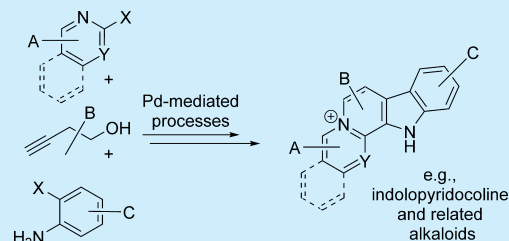
# Sequential Sonagashira and Larock Indole Synthesis Reactions in a General Strategy To Prepare Biologically Active $\beta$ -Carboline-Containing Alkaloids

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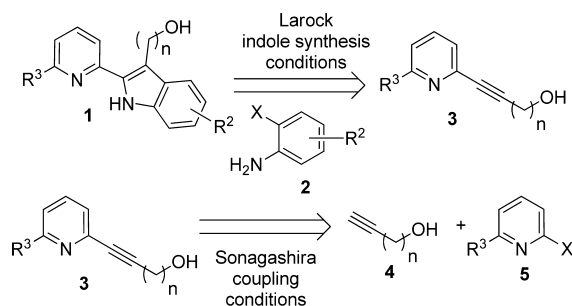
## S Supporting Information

**ABSTRACT:** A general synthetic approach to  $\beta$ -carboline-containing alkaloids was developed. Two consecutive palladium-mediated processes, a Sonagashira coupling and a Larock indole annulation reaction, are central to the method. The scope of the approach was investigated and found to be amenable for constructing a variety of biologically significant natural products and also for preparing substituted analogues for optimization and analysis of their biological properties.



Efficient palladium-mediated reactions allow easy access to highly substituted heterocycles, including indoles, one of the most significant and biologically active core structures in natural products.<sup>1</sup> We sought to apply Larock's method of indole synthesis<sup>2</sup> to prepare 2-pyridyl-indoles **1** by the retrosynthesis shown in Scheme 1. The required Larock

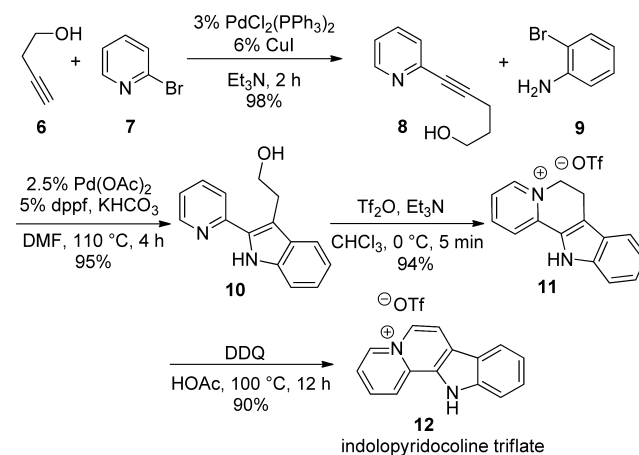
## Scheme 1. Pyridyl Indole Retrosynthesis



substrate **3** would arise from a Sonagashira reaction.<sup>3</sup> An expected advantage of this approach is that each of these consecutive coupling processes would likely tolerate significant structural diversity, a benefit for the optimization of biological activity.

Under optimized Sonagashira conditions butyne-1-ol **6** and 2-bromopyridine **7** give alkyne **8** in nearly quantitative yield (Scheme 2). For the Larock indole annulation reaction the conditions of Senanayake et al.,<sup>4</sup> using bromoanilines rather than iodoanilines and also using only a small excess (1.2 equiv) of the alkyne, were generally suitable. A slight variation gave optimal results: 2.5 mol % Pd(OAc)<sub>2</sub>, 5 mol % 1,1'-bis(diphenylphosphino) ferrocene (dppf), 1 equiv of alkyne, KHCO<sub>3</sub>, DMF, 110 °C, 4 h.<sup>5</sup> Under these conditions the desired indole **10** was obtained in 95% yield with high regioselectivity.<sup>6</sup>

## Scheme 2. Synthesis of Indolopyridocoline Triflate



The hydroxyethyl chain of compound **10** was originally intended to be used for installing diverse groups in the indole C3 side chain. Upon conversion of the alcohol **10** to a tosylate or triflate, a yellow precipitate, tetracycle **11** (Scheme 2), formed instantly. In retrospect this is not surprising, as Gribble and Johnson reported an analogous cyclization of a bromide,<sup>7</sup> while Fürstner et al. also described a similar cyclization of an aldehyde.<sup>8</sup> Optimization of conditions gave compound **11** in 94% yield. The efficiency and ease of operation for this three-step route to compound **11** (88% overall yield with purification by simple filtration) was intriguing, as is the structural similarity of product **11** to a number of biologically significant alkaloids. **11** is the dihydro analog of indolopyridocoline (**12**),<sup>8</sup> a natural product made in 90% yield from **11** through a DDQ-promoted oxidation.

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Alkaloid **11** belongs to a very large family of diverse tetracyclic and pentacyclic natural products (Figure 1) including norketoyobyrine, rutaecarpine, deplancheine, isonauclefidine, javacarboline, and dihydroflavopereirine, structures that have attracted significant synthetic interest.<sup>9</sup>

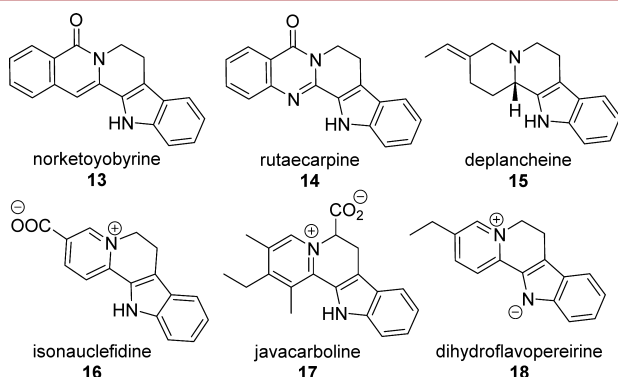
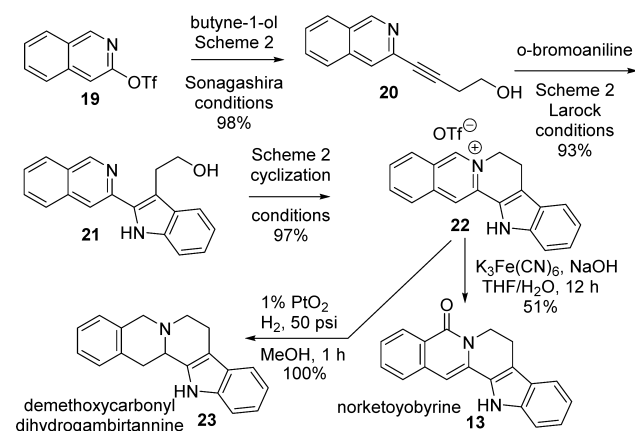


Figure 1. Related  $\beta$ -carboline-containing natural products.

While each step in Scheme 2 is well-precedented, the sequential application of such high-yielding reactions to access members of this class of biologically active alkaloids in a general fashion is noteworthy, especially because it may facilitate rapid structure–activity relationship (SAR) studies in natural product scaffolds. Here, this approach to several members of this family of alkaloids and their substituted analogues is outlined.

A synthesis of the pyridone-containing natural product norketoyobyrine (Scheme 3) tested the generality of the

#### Scheme 3. Syntheses of Pentacycles Norketoyobyrine and Demethoxycarbonyldihydrogambirtannine

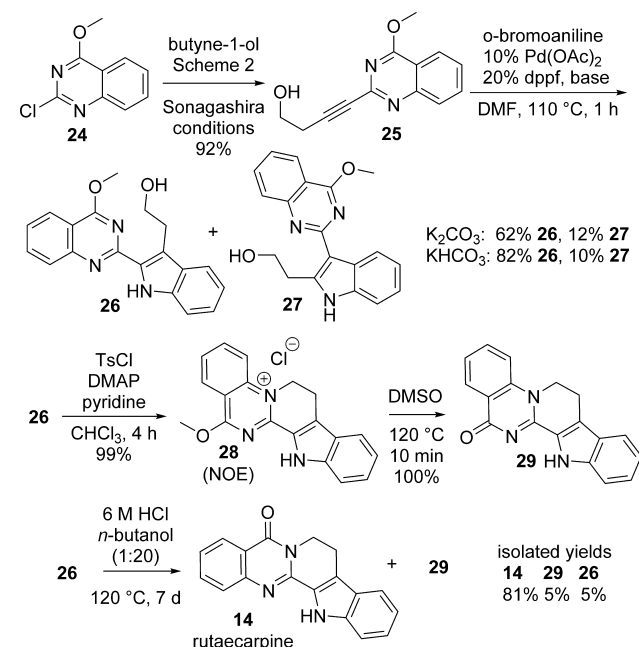


approach. A Sonagashira reaction using isoquinolin-3-yl triflate **19**<sup>10</sup> gave alkyne **20** in nearly quantitative yield. Larock indole synthesis cleanly gave indole isoquinoline **21** and then, upon cyclization, pentacycle **22**. Norketoyobyrine (**13**) was then prepared using a mild oxidation procedure.<sup>11</sup> The intermediate pyridinium salt **22** was also reduced to the known semi-saturated pentacycle **23**.<sup>11</sup>

The synthesis of rutaecarpine tested whether a chloroquinazoline is a suitable substrate for the Sonagashira reaction and also presented the key issue of regioselectivity in the cyclization to a pentacycle (Scheme 4).

Methyl ether **24**,<sup>12</sup> readily prepared in two steps, under Sonagashira conditions smoothly gave alkyne **25**. Larock

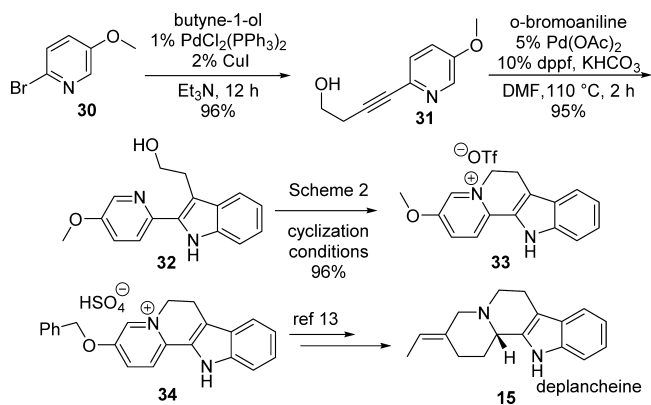
#### Scheme 4. Synthesis of Rutaecarpine



indolization gave a regioisomeric mixture favoring the expected 2-heteroaryl indole product **26**.  $\text{KHCO}_3$  as a base gave an 8:1 preference for **26** in high isolated yield (82%). Tosylate formation prompted pentacycle formation. Interestingly, cyclization proceeded by the attack of the  $\text{N}^1$  rather than  $\text{N}^3$  nitrogen atom of the quinazoline ring, as established by an NOE study of **28**. Chloride-promoted demethylation then quantitatively gave the pentacyclic product **29**, an unknown isomer of rutaecarpine. Cyclization of **26** using  $\text{HCl}/n$ -butanol exhibited preference for rutaecarpine (16:1, 81% yield).

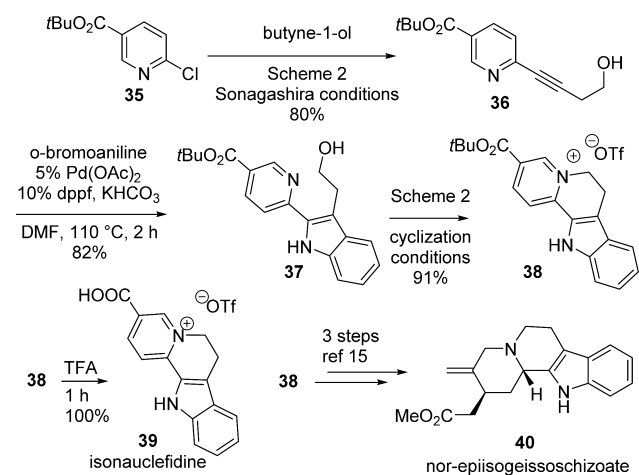
Tetra- and pentacyclic alkaloids with a nonaromatic ring annulated to the indole comprise a significant portion of this extended family of natural products. Often the ring distal to the indole is functionalized, as in deplancheine (Figure 1), which by our methods requires a suitably substituted pyridine as a Sonagashira substrate. As a model, the methoxybromopyridine **30** was found to undergo Sonagashira coupling to give alkyne **31** (Scheme 5). Larock annulation followed by cyclization gave the tetracycle **33** in 88% yield for the three steps. The related benzyl ether **34** has been converted to deplancheine (**15**).<sup>13</sup>

#### Scheme 5. Synthesis of Precursors to Deplancheine



Certain alkaloids require that electron-withdrawing groups be present in the Sonagashira substrate. This is accommodated; *tert*-butyl ester substituted chloropyridine **35** and butyne-1-ol gave alkyne **36** (Scheme 6). A Larock reaction and cyclization

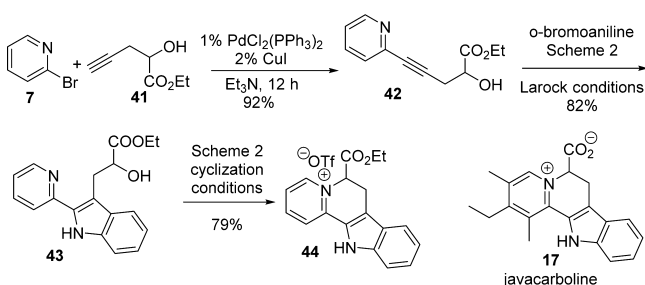
**Scheme 6. Isonauclefidine and Norepiisogeissoschizoate**



gave tetracycle **38**, which was treated with acid to give isonauclefidine triflate (**39**).<sup>14</sup> The conversion of the intermediate tetracycle **38** to norepiisogeissoschizoate (**40**) has also been described.<sup>15</sup>

Substitution in the  $sp^3$  chain that undergoes cyclization is tolerated. Tetracycle **44**, an analog of javacarboline (**17**),<sup>16</sup> was prepared in three steps and 60% overall yield from the alkyne **41**<sup>17</sup> through hydroxyester **43** (Scheme 7).

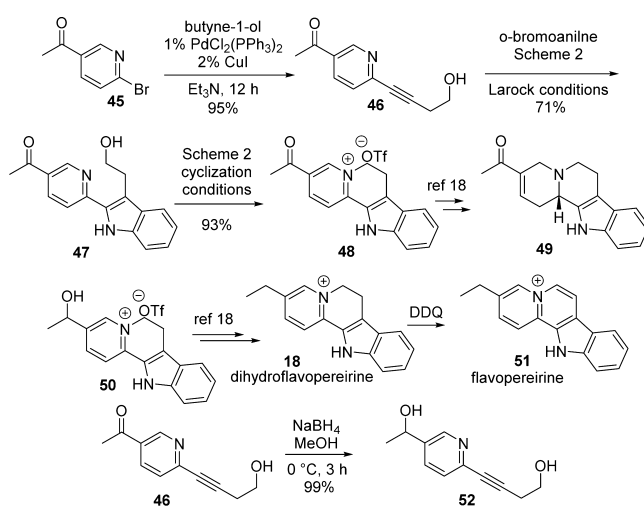
**Scheme 7. Synthesis of an Analogue of Javacarboline**



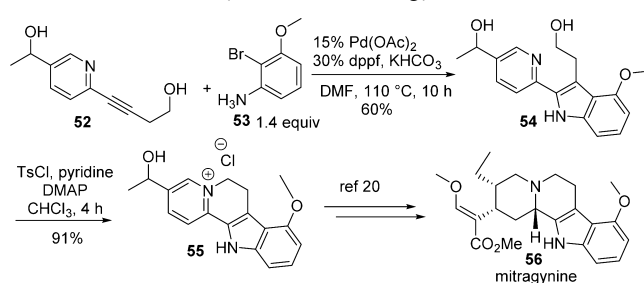
Acetyl bromopyridine **45** (Scheme 8) is also a suitable substrate, giving in three steps a 63% yield of the tetracycle **48**, a known precursor<sup>18</sup> to enone **49**, a building block for heteroyohimbine type alkaloids.<sup>19</sup> The corresponding alcohol **50** has been converted to 6,7-dihydroflavopereirine and flavopereirine.<sup>18</sup> Presumably alcohol **50** would be easily accessed by Larock annulation and cyclization using alcohol **52** or by the reduction of tetracycle **48**. The alcohol **52** indeed undergoes an efficient Larock indole synthesis reaction, as shown by its reaction with the electron-rich aniline **53** to give tetracycle **55**, a precursor in four steps to mitragynine (**56**),<sup>20</sup> a natural product of interest due to its antinociceptive properties (Scheme 9).<sup>21</sup>

Herein is described a general strategy to access tetra- and pentacyclic  $\beta$ -carboline-containing alkaloids, a large family of natural products of great interest in organic synthesis and intriguing for their biological properties. Five natural products

**Scheme 8. Route to Flavopereirines**



**Scheme 9. Formal Synthesis of Mitragynine**



were synthesized: indolopyridocoline, norketoyobyrine, demethoxycarbonyl dihydrogambirtannine, rutaecarpine, and isonauclefidine. Also shown are formal syntheses of norepiisogeissoschizoate and mitragynine as well as methods useful for the synthesis of deplancheine, javacarboline, 6,7-dihydroflavopereirine, and flavopereirine. Key features are sequential Pd-catalyzed coupling reactions, each with significant substrate tolerances. Six substituted pyridine chlorides, triflates, and bromides were suitable Sonagashira reaction substrates (**7**, **19**, **24**, **30**, **35**, and **45**). Two bromoanilines were suitable Larock annulation substrates (**9** and **53**). Substitution in the central ring is allowed (**44**). The wide substrate tolerances suggest that using these methods for the synthesis of arrays of natural product analogs for the optimization of their biological properties and study of their mechanisms of action is feasible and such studies will be the subject of future reports from our laboratory.

## ■ ASSOCIATED CONTENT

### § Supporting Information

Synthesis procedures and the  $^1\text{H}$ ,  $^{13}\text{C}$  NMR spectra, IR spectra, and HRMS data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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- (5) Alternative conditions studied include the use of the bases  $K_3PO_4$ ,  $Cs_2CO_3$ ,  $Na_2CO_3$ ,  $NaHCO_3$ , and  $Et_3N$ . Each was less suitable than  $KHCO_3$  or  $K_2CO_3$ . Catalysts evaluated include  $Pd(PPh_3)_4$ ,  $Pd(OAc)_2/PPh_3$ , and  $Pd(OAc)_2/dppf$ , with the latter reagent giving far better results. Catalyst loading in the range 1–5 mol % gave useful conversions. Reaction times were extended at 1 mol % relative to 2.5 mol % (about 12 h vs 4 h), with slightly lower yields as well (85–91% vs 91–95%).
- (6) The 3-aryl indole regioisomer can, in this case, be detected in small amounts (~2%) by analytical HPLC and LCMS. For the other Larock indole synthesis reactions described in this letter, unless indicated, the regioisomer was not detected or was present in low levels (<5%) and was not isolated.
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