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Total syntheses of 6- and 7-azaindole derived GnRH antagonists

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Abstract—The palladium(0)-catalyzed heteroannulation of a triethylsilyl alkyne and an *ortho*-aminoiodopyridine derivative is used as the key step in a highly convergent route to 6- and 7-azaindoles of biological interest.

In a series of recent reports, we have described the biological activities and the syntheses of a variety of potent GnRH antagonists of the 2-arylindole class.[1] Initially, these structures were prepared via the Fisher indole method,[1,2] but then, ultimately, we were drawn to the elegant approach of Larock.[3,4] During the evolution of this medicinal chemistry effort, we became intrigued at the biological implication of replacing the indole core in one of our more promising lead designs (**1**),[5] with a 6- or 7-azaindole template (**2**; Fig. 1).

We reasoned that Larock's method of indole synthesis may be directly applicable to the preparation of azaindoles. At the onset of our studies, we discovered that this method had indeed been applied to azaindole synthesis, but with only moderate success on relatively simple systems.[6] In spite of the limited literature precedent, we discovered that this transformation could be preparatively useful if $Pd(dppf)Cl_2$ was adopted as the catalyst of choice, and our preliminary results in this area were published recently.[7]

In this report, we describe the synthetic application of this strategy to more sophisticated azaindole systems such as compound **2**. Disconnection of **2** via the Larock transform affords aminopyridine **3** and known alkyne **4** (Scheme 1).[3]

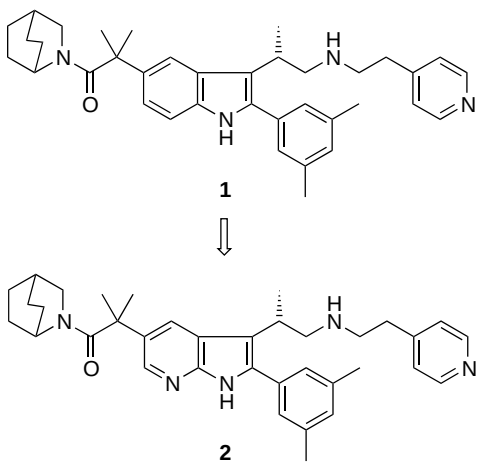
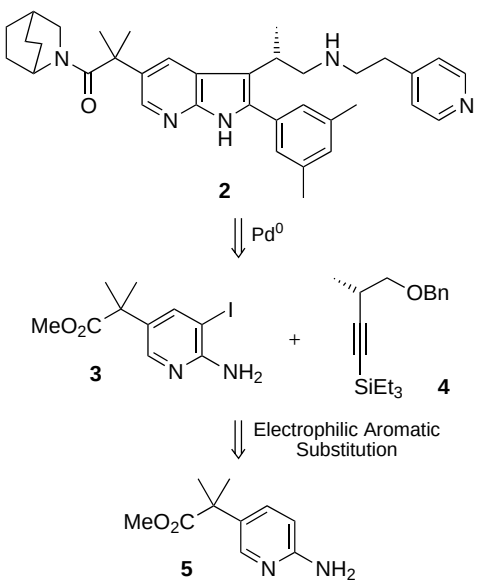


Figure 1.



Scheme 1. Retrosynthetic analysis of 7-azaindole **2**.

Keywords: palladium; heteroannulation; azaindole; 2-aminopyridines.

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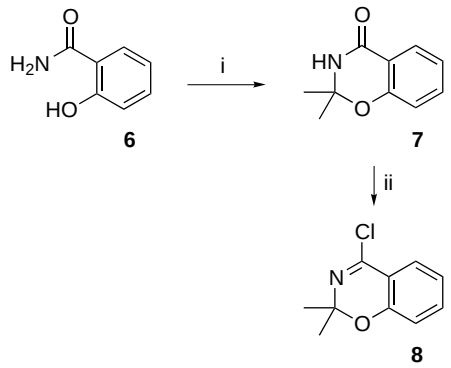
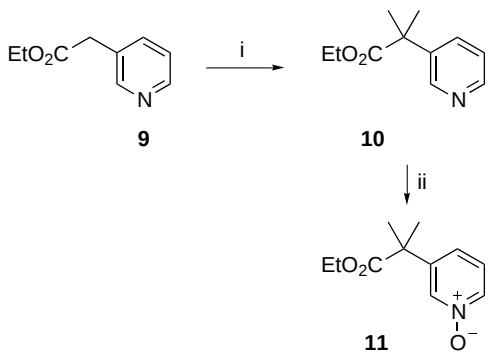
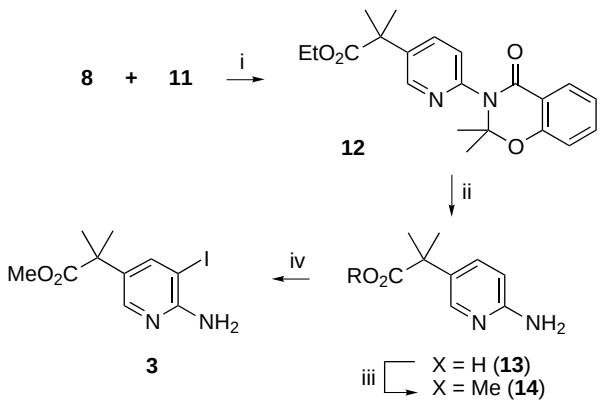
The synthesis of fragment **3** is shown below (Schemes 2–4). Although the Chichibabin reaction was a tempting and potentially expedient entry to systems such as **5**, investigation of the chemical literature revealed that installation of the amino group would not be regioselective, and moreover, the harsh nature of the reaction conditions would likely be incompatible with our resident ester functionality.[8] Instead, we focused our attention to the research of Wachi and Terada who had shown that benzoxazine derivatives of 3-substituted pyridine-*N*-oxides could be rearranged exclusively to 2-amino-5-substituted pyridines.[9] Accordingly, benzoxazine **8** was prepared via the literature route which involved reaction of salicylamide with acetone in the presence of sulfuric acid,[10] followed by chlorination with phosphorous pentachloride in phosphorous oxychloride.[9] In our hands, formation of benzoxazine **7** under the published conditions proved troublesome, with yields ranging from 26 to 37% depending on the reaction scale (literature yield 47%). However, if the reaction was conducted in neat 2,2-dimethoxypropane in the presence of a catalytic amount of pyridinium toluene-4-sulfonate (PPTS), the desired adduct could be obtained in near quantitative yield after recrystallization (Scheme 2).



Scheme 2. *Reagents and conditions*: (i) 2,2-dimethoxypropane, PPTS, 83°C, 15 h, 97%; (ii) PCl_5, $POCl_3$, 50°C, 3 h, 50%.



Scheme 3. *Reagents and conditions*: (i) KHMDS, MeI, rt, 12 h, 83%; (ii) *m*-CPBA, $NaHCO_3$, $CHCl_3$, H_2O, rt, 12 h, 92%.

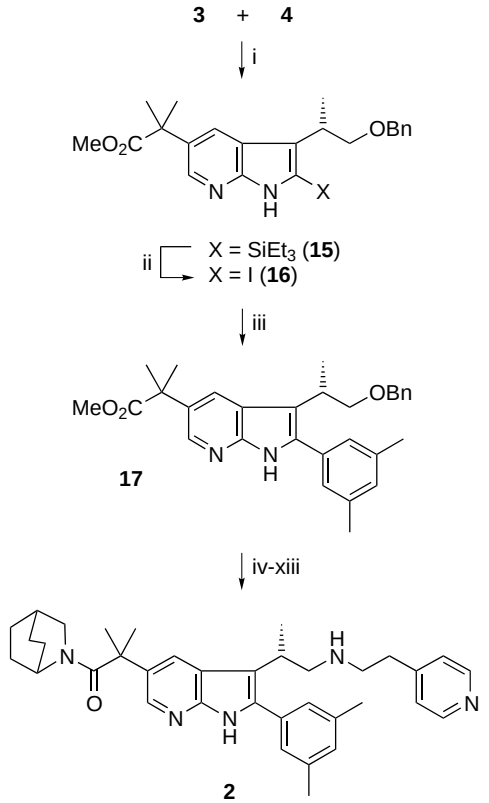


Scheme 4. *Reagents and conditions*: (i) 1,2-DCE, 82°C, 3 days, 84%; (ii) conc. HCl, 100°C, 8 h, 88%; (iii) conc. H_2SO_4, MeOH, 65°C, 15 h, 100%; (iv) I_2, $AgCO_2CF_3$, MeOH, rt, 15 h, 62%.

Pyridine *N*-oxide **11** was also prepared in two steps involving a one-pot base-catalyzed double enolization-double alkylation sequence, followed by *N*-oxidation of the pyridine (Scheme 3).

Reaction of compounds **8** and **11** (2 equiv.) in dichloromethane (DCM) at reflux according to the Wachi and Terada procedure gave the rearranged compound **12** in only 18% yield (Scheme 4). However, we discovered that reaction of **8** and **11** (1 equiv.) in 1,2-dichloroethane (1,2-DCE) at reflux for 3 days resulted in the complete consumption of starting materials to provide **12** in 84% yield. This is in marked contrast to the findings of Wachi and Terada who stipulate that 2 equiv. of *N*-oxide are essential for successful rearrangement, the second equiv. serving as a scavenger for HCl. In our case, HCl is probably liberated from the reaction mixture because of the higher boiling point of 1,2-DCE. Regioselectivity in this step is presumably derived from an unfavorable steric interaction between the 3-substituent of the pyridine and the *gem*-dimethyl moiety of the benzoxazine during the proposed [2,3]-sigmatropic rearrangement. Acid catalyzed hydrolysis[7] and subsequent re-esterification of **13** afforded amino ester **14** in 88% overall yield. Electrophilic aromatic iodination under the influence of silver(I)-assisted catalysis furnished the requisite iodide **3** as a stable colorless solid.

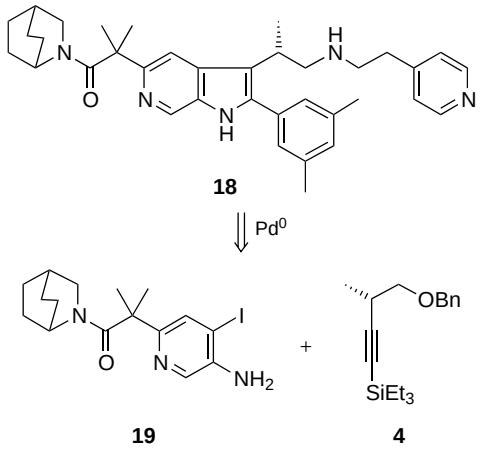
Palladium(0)-catalyzed heteroannulation of alkyne **4** with aminoiodopyridine **3** under the original Larock conditions [$Pd(OAc)_2$, PPh_3, LiCl, Na_2CO_3, DMF, 100°C] gave the desired 7-azaindole **15** in low yield (~10%) together with significant recovery of **3**.[4] However, use of the $Pd(dppf)Cl_2$/LiCl/Na_2CO_3 reagent system resulted in complete consumption of **3** to provide **15** in 95% yield (Scheme 5). [NB. We have observed on a number of occasions that the yield of azaindole product is generally maximized, if the LiCl additive is pre-dried at 100°C, under high vacuum, for approxi-



Scheme 5. *Reagents and conditions*: (i) $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, LiCl, Na_2CO_3, DMF, 100°C 15 h, 95%; (ii) ICl, $AgBF_4$, MeOH/THF, rt, 1 h, 84%; (iii) 3,5-dimethylbenzeneboronic acid, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, 1N Na_2CO_3, EtOH, toluene, 85°C 15 h, >99%; (iv) KOH, MeOH, 65°C, o/n; (v) isoquinuclidine·HCl, PyBOP, NEt_3, CH_2Cl_2, rt, 4 h, 86% (two steps); (vi) $(BOC)_2O$, DMAP, K_2CO_3, CH_2Cl_2, rt, 5 h, 84%; (vii) H_2 (50 psig), $Pd(OH)_2/C$, EtOH, AcOH, rt, 3 days, 92%; (viii) $Zn(N_3)_2 \cdot 2Py$, PPh_3, imidazole, DEAD, CH_2Cl_2, 0°C to rt, 15 h; (ix) H_2 (50 psig), $Pd(OH)_2/C$, EtOH, rt, 15 h, 83% (two steps); (x) 2,4-dintrobenzenesulfonyl chloride, sat. aq. $NaHCO_3$, CH_2Cl_2, rt, 0.5 h, 79%; (xi) 4-(2-hydroxyethyl)pyridine, DEAD, benzene, rt, 1 h; (xii) *n*-$PrNH_2$, CH_2Cl_2, rt, 0.25 h, 90% (two steps); (xiii) TFA, CH_2Cl_2, rt, 6 h, 95%.

mately 1–2 h prior to use in the reaction.[7]] Functional group interconversion to the iodide,[11] followed by palladium(0)-catalyzed arylation with 3,5-dimethylbenzeneboronic acid, afforded the desired 2-aryl-7-azaindole **17** in 80% overall yield. Elaboration of **17** to **2** was accomplished in 10 steps according to a general strategy previously reported.[3]

The 7-azaindole **2** was found to be a very potent GnRH antagonist relative to the indole congener **1**, 'throwing down the gauntlet' for a 6-azaindole variant, i.e. structure **18**. Again we proceeded by way of the reliable and versatile Larock methodology which revealed aminopyridine **19** as our initial synthetic target (Scheme 6).

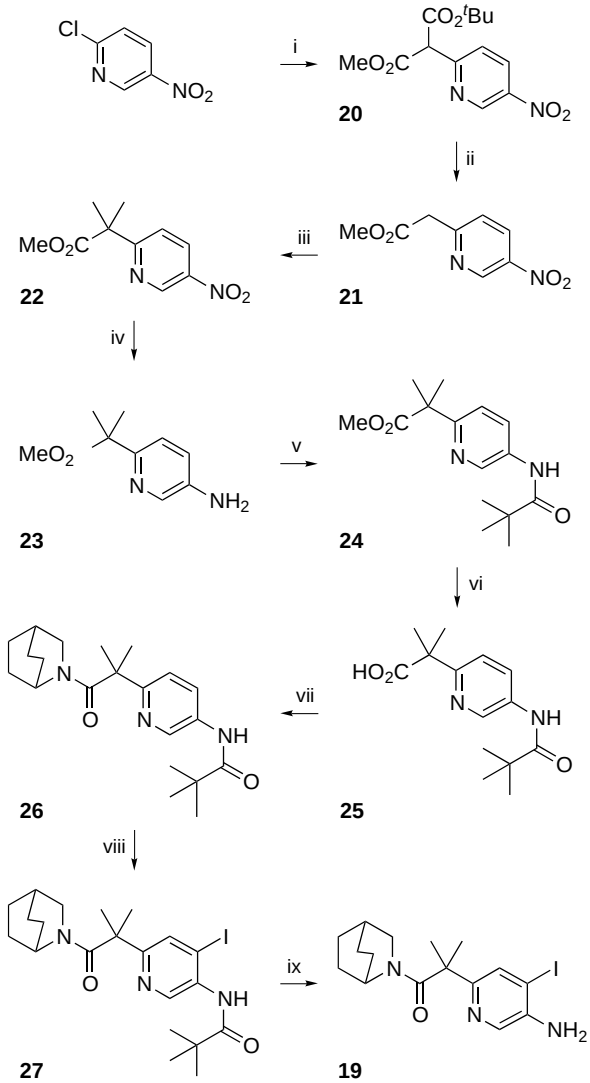


Scheme 6. Retrosynthetic analysis of 6-azaindole **18**.

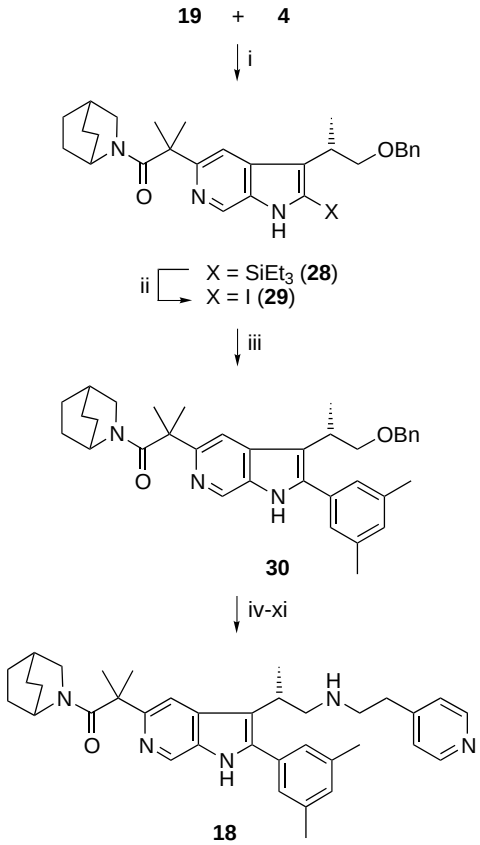
Our synthesis of **19** began with 2-chloro-5-nitropyridine, which was commercially available (Scheme 7). Addition of diethyl malonate, proceeded smoothly, but mono-decarboxylation under either neutral or basic conditions could not be controlled, instead yielding the α-picoline. Addition of the unsymmetrical *t*-butyl methyl malonate and subsequent acid-catalyzed decarboxylation furnished the desired ester (**21**) in good overall yield.[12] Two fold tandem enolization-alkylation gave the *gem*-dimethylcarboxylate **22**. Nitro group reduction, acylation, base-catalyzed ester hydrolysis and amide formation provided diamide **26** in greater than 90% overall yield, without the purification of any intermediates. Directed *ortho*-lithiation with *t*-BuLi under kinetic control, followed by an iodine quench, afforded **27** as the sole regioisomer.[13] Hydrolysis of the sterically less hindered pivaloyl amide functionality furnished the target aminopyridine **19**.

As before, palladium-catalyzed heteroannulation of **4** with **19** using the $Pd(dppf)Cl_2/LiCl/Na_2CO_3$ reagent combination gave a good yield of the desired 6-azaindole (**28**; Scheme 7). Surprisingly, initial attempts to convert the triethylsilyl group to the requisite iodide **29** under a variety of conditions were unsuccessful. Ultimately, we found that exposure of **28** to IPy_2BF_4 in the presence of triflic acid provided **29** in quantitative yield.[14] Suzuki–Miyaura cross-coupling with 3,5-dimethylbenzeneboronic acid proceeded without incident to afford 2-aryl-6-azaindole **30**. The remainder of the synthetic sequence to the final 6-azaindole target **18** was realized according to the literature route (Scheme 8).[3]

In conclusion, the foregoing results have highlighted the viability of the Larock strategy for the construction of challenging azaindole systems. The biological activity of these and other related structures will be reported in due course.



Scheme 7. *Reagents and conditions*: (i) NaH/*t*-butyl methyl malonate, DMF, rt, 5 h; (ii) TFA, DCM, rt, 2 h, 69%; (iii) NaH, MeI, DMF, −20 to 0°C, 15 h, 76%; (iv) Pd/C, H_2, (50 psig), MeOH, 0.75 h; (v) pivaloyl chloride, NEt_3, THF/Et_2O (1:1), 0°C to rt, 0.75 h; (vi) 2.5N NaOH, MeOH, 50°C, o/n; (vii) isoquinuclidine·HCl, PyBOP, NEt_3, CH_2Cl_2, rt, 15 h, 81% (four steps); (viii) (a) *t*-BuLi, THF, −78 to −45°C, 6 h; (b) I_2, THF, −78 to −10°C, 69% (91% based on recovered **26**); (ix) 24% aqueous H_2SO_4, 95°C, 3.5 h, 78%.



Scheme 8. *Reagents and conditions*: (i) Pd(dppf)Cl_2·CH_2Cl_2, LiCl, Na_2CO_3, DMF, 100°C, 15 h, 62%; (ii) IPy_2BF_4, TfOH, CH_2Cl_2, rt, 1.5 h, 98%; (iii) Pd(dppf)Cl_2·CH_2Cl_2, 3,5-dimethylbenzeneboronic acid, 1N Na_2CO_3, EtOH, toluene, 90°C, 15 h, >99%; (iv) $(BOC)_2O$, DMAP, K_2CO_3, CH_2Cl_2, rt, 1 h, 89%; (v) H_2 (50 psig), $Pd(OH)_2$/C, EtOH, AcOH, rt, 2 days, 84%; (vi) $Zn(N_3)_2$·2Py, PPh_3, imidazole, DEAD, CH_2Cl_2, rt, 15 h; (vii) H_2 (50 psig), $Pd(OH)_2$/C, EtOH, rt, 1.5 h, 80% (two steps); (viii) 2,4-dintrobenzenesulfonyl chloride, sat. aq. $NaHCO_3$, CH_2Cl_2, rt, 0.5 h, 90%; (ix) 4-(2-hydroxyethyl)pyridine, DEAD, benzene, rt, 1 h; (x) *n*-$PrNH_2$, CH_2Cl_2, rt, 0.25 h, 60% (two steps); (xi) TFA, CH_2Cl_2, rt, 6 h, 97%.

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