Synthesis of the potent analgesic compound (±)-epibatidine using an orchestrated multi-step sequence of polymer supported reagents

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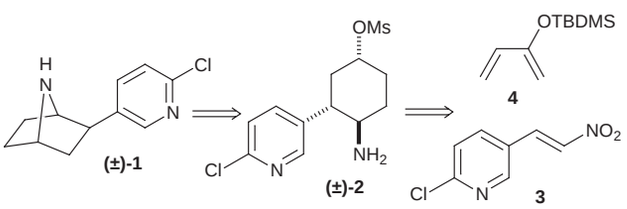
A ten-step synthesis of (±)-epibatidine **1** is described, using an organised array of polymer supported reagents and sequestering agents in a successive manner. No chromatographic purification steps are required to afford the product in >90% purity.

In the previous paper, we described the preparation of a natural product using an orchestrated sequence of polymer supported reagents to effect all of the individual synthetic steps.[1] Here we extend these ideas to a longer reaction sequence leading ultimately to the synthesis of (±)-epibatidine **1**, a potent analgesic compound isolated from the Ecuadorian poison frog *Epipedobates tricolor*.[2]

As in the previous work, no chromatography steps were necessary and all stages proceeded with minimum optimisation in excellent yields. Moreover, the intermediates could be isolated and diverted for use in other combinatorial programmes.

Our route to epibatidine **1** utilised a precedented transannular 1,4-disconnection to the corresponding amino mesylate **2**.[3] This in turn could be assembled *via* a Diels–Alder reaction[3d] between alkene **3** and a silyl protected 2-oxadiene **4** as shown in Scheme 1.



Scheme 1

Treatment of the commercially available acid chloride **5** with polymer supported borohydride[4] at room temperature cleanly afforded the corresponding alcohol **6** in good isolated yield (Scheme 2). A number of protocols were investigated for the oxidation of **6** to the pyridyl aldehyde **7**. The polymer supported perruthenate[5] (PSP) and polymer supported permanganate[6] (PSM) reagents introduced by our group as well as polymer supported (diacetoxyiodo)benzene[7] were found to be extremely efficient for this process with no over-oxidation to the corresponding carboxylic acid being observed. Alternative 'clean' oxidants such as Magtrieve[8] (magnetised CrO_2 filaments) were also suitable for this reaction, however, reaction times were considerably longer under similar reaction conditions.

A basic Amberlite resin (IRA420-OH^- form) was found to be a suitable base for the Henry reaction between aldehyde **7** and nitromethane.[9] Removal of the resin by filtration and evaporation of excess nitromethane afforded the unstable nitro alcohol **8**. Derivatisation with trifluoroacetic anhydride cleanly afforded the corresponding acetate, with trifluoroacetic acid and excess trifluoroacetic anhydride being simply removed *in vacuo*. Treatment with dimethylaminomethyl polystyrene resin in CH_2Cl_2 at room temperature prompted elimination to give exclusively (>95% by 400 MHz ^{1}H NMR) the *trans* alkene **3**. Reactions were monitored by LC-MS which indicated product purity of >95% in all steps *en route* to alkene **3**. High field NMR analysis confirmed >95% purity for all intermediates.

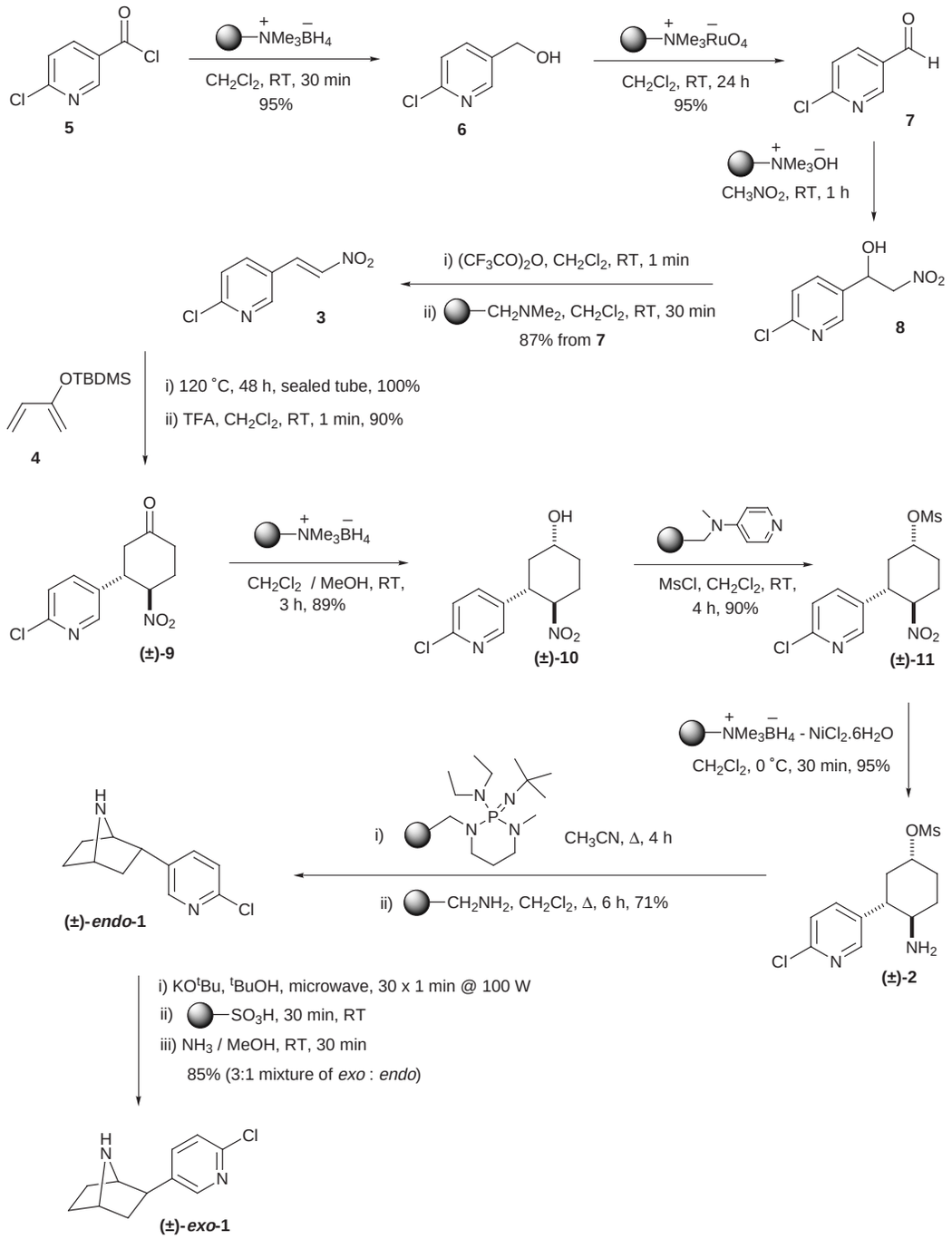
In an important modification, it was found that by encapsulating quantities of the polymer supported reagents in sealed porous pouches, the reaction sequence of acid chloride **5** to alkene **3** could be carried out in a one-pot procedure. When a reaction was judged to have gone to completion (TLC, LC-MS), the pouch was simply removed, washed with solvent and the next reagent-containing pouch was added to the flask. This removed the need for filtration between individual steps.[10]

With quantities of the alkene **3** in hand, construction of the cyclohexyl ring system was attempted *via* a thermal Diels–Alder reaction. Heating of two equivalents of a TBDMS protected 2-oxadiene **4** with alkene **3** in toluene in an undried, sealed vial at 120 °C reproducibly afforded quantitative yields of the TBDMS protected Diels–Alder adduct. Removal of the excess diene *in vacuo* followed by TFA catalysed hydrolysis of the silyl enol ether afforded the ketone **9** with exclusively the *cis* geometry.

Reduction of the ketone **9** with polymer supported borohydride[4] gave a 7:1 diastereomeric ratio in favour of the all equatorial substituted cyclohexanol **10**. Conversion of the alcohol **10** to the corresponding mesylate **11** was acheived by adding a solution of the alcohol in CH_2Cl_2 to a preformed mixture of polymer supported aminomethylpyridine[11] and mesyl chloride and stirring at room temperature.

Reduction of the aliphatic nitro functionality of mesylate **11** with retention of configuration initially proved problematic as in previous reports,[3m,12] where the lability of the 2-chloro substituent of the pyridyl ring frustrated a range of attempted hydrogenation (Rh/Al_2O_3, Pd/C,[13] PtO_2[14]) and transfer hydrogenation (HCO_2NH_4, Pd/C[15]) protocols. However, using Raney Nickel as catalyst with an atmospheric pressure of hydrogen, the transformation could be accomplished without concommitant reductive dechlorination of the pyridyl ring, albeit with extended reaction time.[16] The best method for this transformation proved to be the use of polymer supported borohydride with $NiCl_2 \cdot 6H_2O$.[17] This reproducibly furnished the desired amino mesylate **2** rapidly and under mild conditions and was found to be superior to the use of $NaBH_4$ with $NiCl_2$ under the usual reduction conditions.[18]

The commercially available polymer supported phosphazene base[19] allowed the key transannular cyclisation to proceed in higher yield and more rapidly than under the thermal conditions (toluene, Δ, overnight, 46%) previously reported.[3g,j] As no trace of the potential by-product arising from intermolecular



Scheme 2

amino-mesylate displacement was observed in these reactions (LC-MS, ^{1}H NMR), the most significant impurity remaining was the epimeric *cis* amino mesylate of **2** (≈10%). This is derived from the minor diastereomer obtained from the reduction of **9** to **10** and has the incorrect configuration for cyclisation. This, and any acidic impurities, were conveniently removed by sequestration with a basic aminomethyl polystyrene resin which effected an intramolecular displacement of the mesylate to remove the unwanted diastereomer of **2** from solution. Filtration afforded the *endo* isomer of **1** in >85% purity by LC-MS.

The final step in the synthetic sequence required the epimerisation of the α-pyridyl proton to give the thermodynamically more stable *exo* isomer of epibatidine **1**. Previous reports indicated that even under forcing conditions (^{t}BuOK, ^{t}BuOH, Δ, 30 h, 50%), this reaction could not be driven beyond 50% completion [3c,f,g,12b,20] and chromatographic separation of the *endo* and *exo* isomers was required. In contrast, we have found that use of microwave irradiation using a Labwell Microwell 10 system in a sealed vessel allowed conversion to a 3:1 ratio in favour of the desired *exo* isomer of **1** in much reduced reaction times (30 min). Reaction work-up involved sequestering both the potassium salts and the product amine **1** onto an acidic ion-exchange resin (A15) and discarding the resultant solution containing only neutral impurities. The product was then displaced from the resin by treatment with NH_3/MeOH to afford epibatidine **1** in >90% purity (LC-MS, ^{1}H NMR) as a 3:1 mixture of *exo*:*endo* isomers after the ten-step linear sequence.

We believe that the above sequence not only demonstrates the power of using orchestrated multi-step polymer supported reagents in synthesis, but points the way towards the assembly of more complex targets using even longer routes. With the ever increasing range and availability of supported reagents, both linear and convergent sequences can be envisaged that could deliver truly large arrays of functionalised molecules in a very

rapid and efficient fashion. We believe the opportunities for these systems are enormous.

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