Synthesis of the alkaloids (±)-oxomaritidine and (±)-epimaritidine using an orchestrated multi-step sequence of polymer supported reagents

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The concise synthesis of the alkaloids (±)-oxomaritidine **1** and (±)-epimaritidine **2** in high yield are described, which employs a sequence of five- and six-step reactions respectively, using solely polymer supported reagents in an orchestrated successive manner.

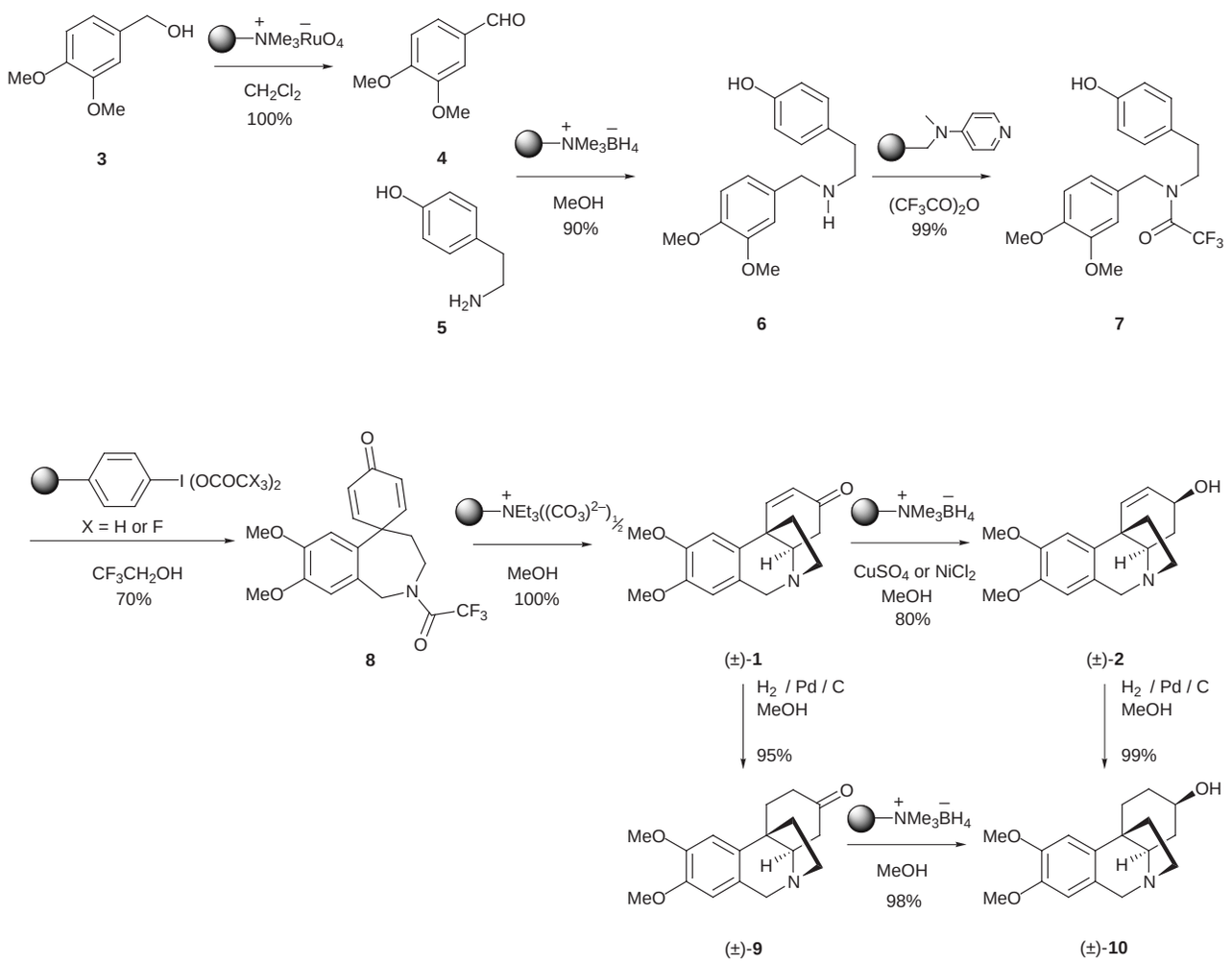
We have recently challenged the current dogma of preparing compound libraries on solid supports preferring instead to combine the advantages of solution phase chemistry with the versatility and convenience of polymer supported reagents.[1] Here, we demonstrate that these concepts are readily adapted to natural product synthesis, by effecting the clean and efficient preparation of the alkaloids (±)-oxomaritidine **1** and (±)-epimaritidine **2**. These compounds were obtained, in a linear sequence of reactions, using five and six polymer supported reagents respectively, with work-up simply involving filtration followed by evaporation of solvent. To the best of our knowledge, this report and the following paper[2] constitute the first total syntheses of natural products using a sequence of polymer supported reagents.

Following a modification of a route recently described by Kita,[3] which allowed access to galanthamine-type amaryllidaceae alkaloids, we have devised a complementary route using *polymer supported reagents* in order to accomplish these syntheses. The first step (Scheme 1) employed polymer supported perruthenate (PSP) reagent[4] which converted the alcohol **3** into the aldehyde **4** in essentially quantitative yield. This aldehyde was reacted with the primary amine **5** under reductive amination conditions to generate the norbelladine derivative **6** in excellent yield, any by-product or unreacted materials, in this step, being absorbed onto the polymer which was simply filtered off at the end of the reaction. Optimum conditions for this step involved adding the polymer supported borohydride[5] reagent to a solution of the pre-formed imine. Alternatively, performing reactions using polymer supported cyanoborohydride,[6] under conditions we had developed previously,[1c] resulted in similar clean and quantitative conversions to the secondary amine **6**. Subsequently, trifluoroacetylation of this amine **6** was effected by treatment with trifluoroacetic anhydride using polymer bound aminomethyl pyridine[7] to give the amide **7** in 99% yield. The intramolecular phenolic oxidative cyclisation of **7** to the spirodienone **8** was best achieved using polymer supported (diacetoxyiodo)benzene[8] in trifluoroethanol, although reactions with polymer supported [bis(trifluoroacetoxyiodo)]benzene[9] reagent gave comparable results. This oxidation reaction gave the desired regioisomeric *para–para′* coupled product **8** in 70% yield with no other products being detected by LC-MS following filtration and evaporation. Finally, treatment of the trifluoroacetamide **8** with polymer supported carbonate[10] in methanol resulted in rapid deprotection and spontaneous intramolecular 1,4-addition to give (±)-oxomaritidine **1** as a crystalline product in 98% yield which was identical to the previously prepared material[11] by mp, NMR and MS analysis. Reduction of the carbonyl group in **1** using polymer supported borohydride, in the presence of a catalytic quantity of $NiCl_2 \cdot 6H_2O$ or $Cu(SO_4)_2 \cdot 5H_2O$[12] in methanol, provided access to the natural product (±)-epimaritidine **2** in high yield, also identical to authentic material[11] by NMR and MS analysis.

The route described above could be readily modified to prepare other novel analogues of **1** and **2** or alternatively scaled-up to give material which would be highly suitable for further combinatorial change. In addition, we have prepared two other members of the amaryllidacae family of alkaloids, and in the process confirmed the stereochemical outcome of the reduction step in the transformation of (±)-**1** into (±)-**2**. Initially, catalytic hydrogenation of **1** provided (±)-dihydrooxomaritidine **9** in 95% yield. This was further reduced with polymer supported borohydride in methanol to afford (±)-epidihydromaritidine **10**. Subsequent catalytic hydrogenation of **2** followed by filtration through a small pad of Celite, as in the transformation from **1** to **9**, gave the same product **10**. Spectroscopic data were consistent with those previously published[13] and the relative stereochemistry of the hydroxy group was confirmed by NOE measurements.

In the following paper[2] a longer and more elaborate reaction sequence is described which opens up even greater opportunities for the use of polymer supported reagents in organic synthesis.

In summary, the preparation of two natural products (±)-oxomaritidine **1** and (±)-epimaritidine **2** has been achieved in excellent overall yields and high purity. The reaction sequences, which provided these compounds, were conducted entirely using polymer supported reagents without recourse to conventional work up procedures or the need for chromatographic purification. Moreover this approach has considerable potential for the preparation of other members of the amaryllidaceae family and following our linear route (±)-dihydrooxomaritidine **9** and (±)-epidihydromaritidine **10** were prepared in six and seven steps respectively without chromatography.



Scheme 1

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