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Total Synthesis of 2-(2-Ketoalkyl)-piperidine Alkaloids (+)-Pelletierine, (+)-Haloxynine and (-)-*N*-Methyl-pelletierine via Regioselective Wacker Oxidation

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Dedicated to Dr. J.K. Kirtany on the occasion of his 75th birthday

A practical synthesis of naturally occurring piperidine alkaloids (+)-pelletierine, (+)-haloxynine and (-)-*N*-methyl-pelletierine is described from (-)-pipecolinic acid using Wittig reaction and Wacker oxidation as the key steps. The protocol exploits the regioselective oxidation of the internal olefins.

Introduction

Piperidine alkaloids having a substituent at 2-position are found ubiquitously in nature and as a key part structure in many drug molecules (Figure 1).[1] These alkaloids have gained immense importance in the field of pharmacology due to their wide range of biological activities.[2] For example (+)-pelletierine **1a** and (-)-*N*-methyl-pelletierine **2** isolated from the roots of *Punica Granatum* (pomegranate) have been of considerable interest to the organic chemists owing to their use as an anthelmintic.[3] Another alkaloid (-)-halosaline **3** along with (-)-haloxynine **4** isolated[4] from the desert plant *Haloxylon salicornicum* displays antidiabetic[5] and anthelmintic[6] properties respectively. (+)-Sedridine **7** isolated from *sedum acre* has been employed for the treatment of bronchitis, pneumonia and asthma.[7] Several piperidine alkaloids are also being utilized as promising drug candidates. For example, D-threo-methylphenidate (Ritalin) **5** is commonly employed[1a] in psychotropic medication, which affects the emotions, mind, and behavior of a person to overcome attention deficit hyperactivity disorder (ADHD). Another important drug, (–)-perhexiline **6** is being used as a therapeutic agent[1b,c] for the treatment of various cardiovascular diseases.

Pelletierine has been suggested as a precursor for the biosynthesis of many alkaloids. It has been used as a key intermediate in the biomimetic synthesis of several alkaloids. Pelletierine is also used in chemical synthesis of various

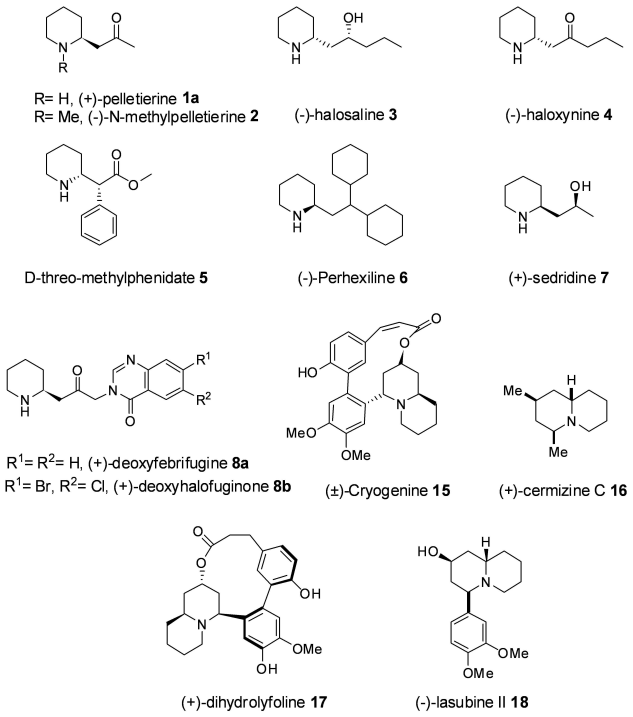

Figure 1. Biologically important piperidine alkaloids and drug candidates

complex 2-substituted piperidine alkaloids like (±)-cryogenine**15**, (+)-deoxyfebrifugine **8a**, (+) deoxyhalofuginone **8b**, (+)-cermizine C**16**, (-)-5-epi-dihydrolyfoline, (+)-dihydrolyfoline **17** and(-)-lasubine II **18**.[8] Therefore, asymmetric synthesis of 2-substituted piperidine alkaloids has been the target of many laboratories. Various strategies employed for the synthesis include chiral pool,[9a] readily available chiral nitrogen compounds,[9b] organocatalytic aminoxylation,[9c] aza-Michael reaction,[9d,e] aza-Henry reaction,[9f] aza-Diels-Alder,[9g] chiral auxiliary approach,[9h,i] transition metal catalyzed reactions,[9j] Mannich reaction[9k] and chiral bases.[9l] From our laboratory, we have reported a few chiral syntheses of pyrrolidine and piperidine alkaloids.[10] In continuation of that, we herein report the synthesis of (+)-pelletierine **1a** and its analogs from commercially available (-)-pipecolinic acid **11**.

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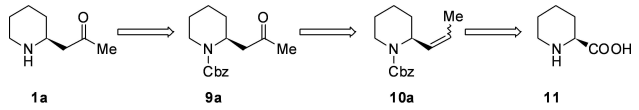
Results and Discussion

Our approach towards the synthesis of (+)-pelletierine 1a and its analogs were envisaged via the retrosynthetic analysis shown in scheme 1. Accordingly, our strategy includes the



Scheme 1. Retrosynthetic analysis

formation of olefin 10a and the keto compound 9a via Wittig olefination and regioselective Wacker process, respectively. Earlier we had reported the synthesis of five-membered pyrrolidine alkaloid (-)-hygrine and (-)- norhygrine from (-)-proline via regioselective Wacker oxidation in the presence of Cbz protecting group.[10f] Mitsudome, T. *et al.* have also reported the synthesis of Cbz protected hygrine, which involves the simple catalytic system consisting of $PdCl_2$ and N,N-dimethylacetamide enabling the clean and regioselective synthesis of ketones.[11] We thought that it should be possible to extend the same protocol for the synthesis of piperidine alkaloids. However, we needed to validate the regioselectivity of Wacker oxidation next to a six-membered ring.

During the Wacker reaction, the olefin 10a would prefer to be in conformation II over I due to $A^{1,3}$ interactions and water molecule could then attack from the less hindered position to give the required keto functionality regioselectively as depicted in Figure 2.

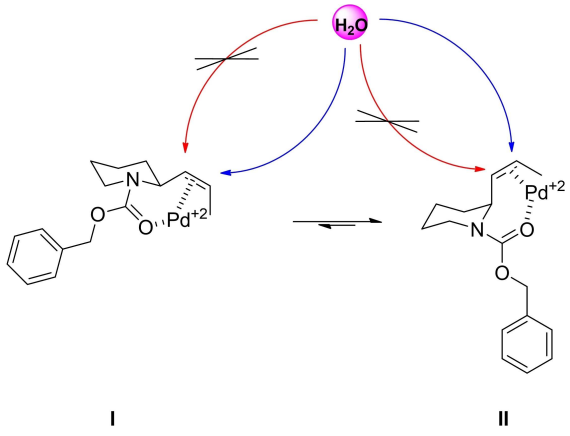
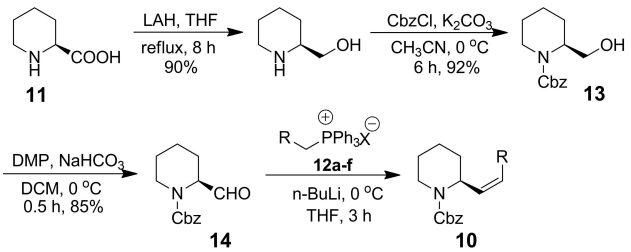


Figure 2. Prediction for the attack of water on the Palladium complex.

We commenced our synthesis with the preparation of (*S*)-carbobenzyloxypipecolinol **13** from commercially available (*S*)-pipecolinic acid **11** by the procedure mentioned in the literature.[12,10b] The pipecolinol **13** was subjected to DMP oxidation followed by Wittig reaction with the corresponding phosphonium salts **12a-f** to obtain the olefins **10a-f** (Scheme 2). The Wittig reaction gave consistently good yields irrespective of the chain length of the phosphoranes with



Scheme 2. Synthesis of olefins **10a-f**

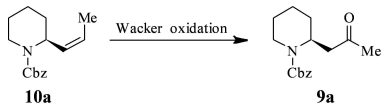
predominantly *Z* isomer in case of unstabilized ylides (**12a-c,e,f**) and a mixture of *E:Z* isomers in case of semi-stabilized ylide (**12d**) as observed by ^{1}H NMR analysis (Table 1).

Table 1. Wittig reaction utilizing different phosphonium salts

Phosphonium salt	R	Product	Ratio(*E:Z*)[a]	Yield (%)
12a;$C_2H_5PPh_3^+I^-$	Me	10a	Traces of E	71
12b;$C_3H_7PPh_3^+Br$	Et	10b	Traces of E	74
12b;$C_3H_7PPh_3^+Br^-$	Pr	10c	Traces of E	72
12d;$C_7H_7PPh_3^+Cl^-$	Ph	10d	4:6	73
12e;$C_4H_9PPh_3^+Br^-$	i-Pr	10e	Traces of E	74
12f;$C_9H_{11}PPh_3^+Br^-$	C_8H_9	10f	Traces of E	70

[a]Ratio based on ^{1}H NMR

Initially, the olefin **10a** was subjected to traditional Wacker-Tsuji oxidation (scheme 3) which as expected provided the regioselectively Cbz-protected pelletierine **9a** in 70% yield.



Scheme 3. Wacker oxidation on the olefinic compound 10a

To optimize the yields of the Wacker process, several reaction conditions were tried (Table 2). Kaneda, K. *et. al.*, from

Table 2. Optimization studies for Wacker oxidation

Entry	Reaction condition	Yield (%)
1	$PdCl_2$, CuCl, 1 atm O_2 DMF: H_2O (8:2) 8 h, 80 °C	70
2	$PdCl_2$, 1 atm O_2 DMA: H_2O (8:2) 8 h, 80 °C	13
3	$PdCl_2$, CuCl, 1 atm O_2 DMA: H_2O (8:2) 8 h, 80 °C	74
4	5 mol% $Pd(OAc)_2$ 1.5 equiv. DMP CH_3CN: H_2O (7:1) 50 °C, 5 h	84

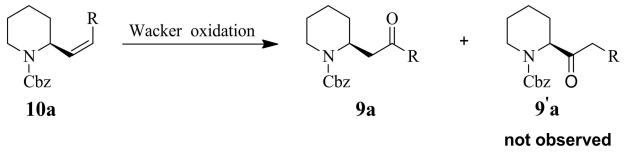
the studies of cyclic voltammetry and X-ray absorption fine structure (XAFS) have proved that N,N-dimethylacetamide (DMA) acts as the most effective solvent[13,14] for enhancing the reoxidation of Pd(0) to Pd(II) by molecular oxygen without the need of additional co-oxidant (CuCl). The method also promotes the stabilization of palladium catalyst without precipitation into inactive metal. When this system was used for the Wacker process (entry 2), **9a** was obtained in only 13% yield. Hence, we carried out the oxidation using co-oxidant using the catalytic system as shown in entry 3, which afforded the desired keto compound in 74% yield. Using the same condition, we carried out Wacker oxidation of other olefins **10b-g**. It was observed that the olefins **10b** and **10c** gave the required keto products in 51% and 46% yield respectively but the olefins **10d** and **10e** gave only trace quantities of ketones. Compound **10f** was obtained in only 38% yield. Recently, there are many Wacker oxidation reports which include modification of the catalyst to make the Wacker process milder and more efficient.[15] Fernandes *et al.* have revealed an operationally simple and scalable method to mimick the Wacker protocol. The process involves a combination of hypervalent iodine species (DMP) and Pd(II) to generate the methyl ketones.[15b] Gratifyingly when this protocol was tried on **10d**, it provided the required Cbz protected norsedaminone **9d** in 42% yield. Hence, Fernandes's protocol was used for further studies (Table 3).

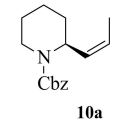
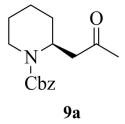
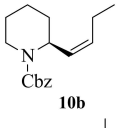
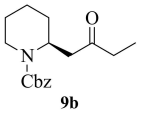
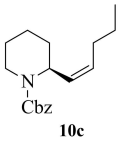
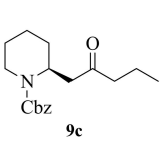
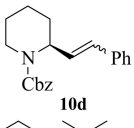
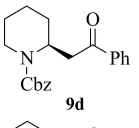
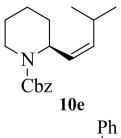
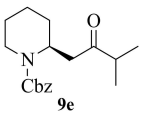
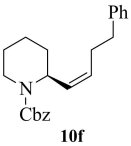
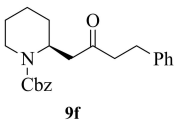
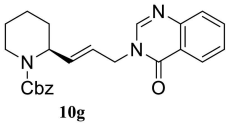
Cbz-protected pelletierine was obtained in 84% yield. β-Keto amine **9b** was obtained in 71% yield whereas the keto compound **9c** was obtained in 62% yield. Also the keto compounds **9e** and **9f** were obtained in satisfactory yields. We then attempted the synthesis[9k] of antimalarial quinazoline alkaloid analogue, (+)-deoxyfebrifugine **8a** via the Wacker oxidation of the corresponding olefinic compound **10g** but we couldn't get the expected keto compound (Cbz-protected deoxyfebrifugine) as the reaction mass turned into a complex mixture.

From the ^{1}H NMR studies, it was possible to assign the regioselectivity obtained for the products. For example, Cbz-protected haloxynine **9c** showed four protons in the range δ 2.64-2.33 which indicated the methylene protons (H_a and H_b) next to the carbonyl group of the side chain (figure 3). These observations stipulated that the other regioisomers **9′b-f** were not obtained. The Cbz protecting group, due to its steric bulk plays a vital role in the targeted regioselectivities.

The intended natural products were then obtained by hydrogenolysis of the respective Cbz-protected β-keto amines. (+)-Pelletierine **1a** was obtained by hydrogenolysis of **9a** whereas (-)-*N*-methyl-pelletierine **2** was obtained via reduction with lithium aluminum hydride followed by DMP oxidation (Scheme 4). (+)-Haloxynine **1c** and (*S*)-1-(piperidin-2-yl)butan-2-one **1b** were obtained by hydrogenolysis of **9c** and **9b**, respectively (Table 4). The physical and spectroscopic data of the intermediate and final compounds matched very well with the literature data. To the best of our knowledge, there are only three reports available on the synthesis of haloxynine of which two deal with the racemic mixture[16,6] and one demonstrates diastereoselective [3 + 2] dipolar cycloaddition.[9i]

Table 3. Wacker oxidation on various olefins under optimized conditions.



Sr. No.	*N*-Cbz Protected olefin	β-Keto amine	Yield (%)
1	 10a	 9a	84
2	 10b	 9b	71
3	 10c	 9c	62
4	 10d	 9d	42
5	 10e	 9e	45
6	 10f	 9f	54
7	 10g		Complex Mixture[a]

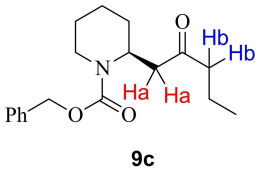
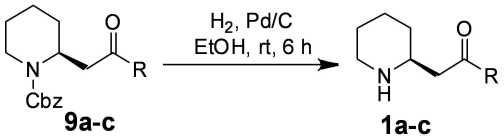
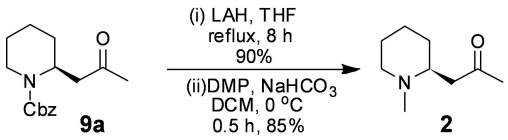


Figure 3. Cbz-protected haloxynine

Table 4. Synthesis of β-keto amines



Entry	Product	Yield (%)
1	1a; R = Me; (+)-Pelletierine	78
2	1b; R = Et	74
3	1c;R = Pr; (+)-Haloxynine	76



Scheme 4. Synthesis of (-)-*N*-Methyl-pelletierine

Conclusions

In summary, we have developed an efficient method for the synthesis of biologically important piperidine alkaloids containing a β-keto functionality using Wittig reaction and regioselective Wacker oxidation. We believe that this protocol can be utilised for the synthesis of a wide range of natural products containing a β-keto amine framework. The usefulness of the method was demonstrated by the synthesis of natural products like (+)-pelletierine, (+)-haloxynine and (-)-*N*-methyl-pelletierine.

Supporting Information summary

Supporting Information contains details about synthetic procedures, experimental data and soft copies of NMR-spectra.

Acknowledgments

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: (+)-Haloxynine · (+)-Pelletierine · Piperidine alkaloids · Wacker oxidation · Wittig reaction

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