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Concise Total Synthesis of (±)-Maritidine

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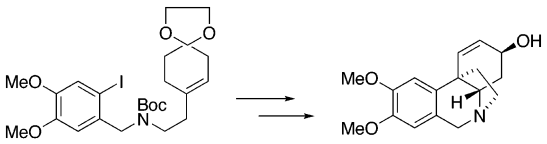
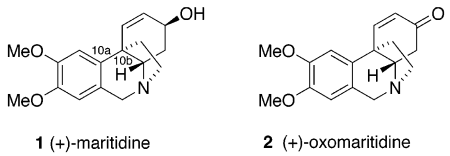
ABSTRACT



Maritidine can be readily obtained from the corresponding protected β,γ-unsaturated ketone. The quaternary carbon of maritidine was created for the first time via an intramolecular Heck reaction.

Maritidine alkaloids[1] have been found to possess cytotoxic properties (Figure 1).[2] These *Amaryllidaceae* alkaloids



1 (+)-maritidine **2** (+)-oxomaritidine

Figure 1.

display a spiro quaternary carbon. The incorporation of this quaternary center is the critical element in the total synthesis of maritidine-type alkaloids. Because of their limited availability from natural sources,[3] several syntheses of these compounds have been reported employing a biomimetic intramolecular phenolic oxidative cyclization as the crucial step in the formation of the tetracyclic framework.[4] However, the quaternary carbon of dihydromaritidine (**3**) has been previously created by different approaches involving long multistep sequences.[5] It should be noted that to date it is not possible to oxidize (±)-dihydromaritidine (**3**) to maritidine (**1**) (Figure 1).

In our synthetic pathway, we planned to use for the first time an intramolecular Heck reaction for the construction of the quaternary center of the *Amaryllidaceae* maritidine-

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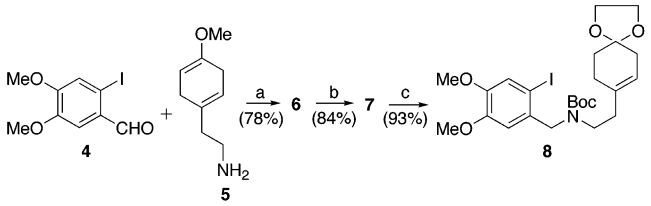
type alkaloids. Our strategy was to form the key connection bond between the C10a−C10b carbons of the target molecule (**1**) by an intramolecular Heck reaction to access the spiro tricyclic dienone (**11**), which could then be used as a valuable precursor of (**2**) and (**1**). The intramolecular Heck reaction leading to 7-exo trigonal cyclization has not often been described.[6] This process has rarely been used for the creation of a spiro quaternary center.[7]

The synthesis started with the known aryl iodide (**4**)[8] and amine (**5**).[9] Reductive amination of these two components followed by protection of the enol ether function gave amine (**7**). Subsequent protection of the amine function with di-*tert*-butyl dicarbonate furnished compound (**8**) (93%), the precursor for the intramolecular Heck reaction (Scheme 1).

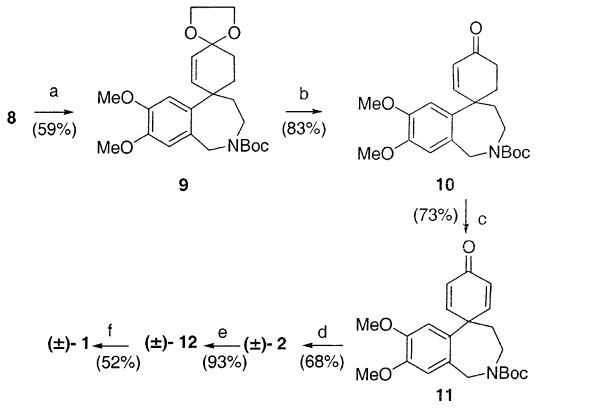
Scheme 1[a]



[a] Conditions: (a) $NaBH_4$, MeOH, rt. (b) $(CH_2OH)_2$, $BF_3{\cdot}Et_2O$, THF, rt. (c) Boc_2O, ^{t}BuOH/H_2O 1/1, rt.

The key carbon bond-forming reaction was achieved in 59% yield by heating (**8**), catalytic amounts of 10% [Pd_2dba_3], 20% dppe, and thallium acetate (1.2 equiv) in acetonitrile.[10] After removal of the dioxolane group of (**9**) with hydrochloric acid to give (**10**) (83%), oxidation of the α,β-unsaturated ketone function of the latter to the corresponding dienone (**11**) was accomplished in 73% yield by using selenium dioxide and acetic acid in ^{t}BuOH. Removal of the N-Boc group of (**11**) with trifluoroacetic acid resulted in spontaneous cyclization to afford oxomaritidine (**2**) (68%). Enone (**2**) was stereoselectively reduced with the combined reagent sodium borohydride−cerous chloride[11] to give epimaritidine (**12**) (93%). Finally, the allylic alcohol of (**12**) was converted to the corresponding mesylate and inverted by displacement with cesium acetate. The resulting acetate was saponified with potassium carbonate and methanol to give (±)-maritidine (**1**) (52%), which had spectral data in accordance with published values (Scheme 2).[4]

Scheme 2[a]



[a] Conditions: (a) [$Pd_2(dba)_3$], dppe, TlOAc, CH_3CN, reflux, 3 days. (b) 1 N HCl, THF, rt. (c) SeO_2, ^{t}BuOH, AcOH, reflux. (d) CF_3CO_2H, CH_2Cl_2, rt. (e) $NaBH_4$, $CeCl_3$, MeOH, rt. (f) (i) MsCl, NEt_3, CH_2Cl_2, rt; (ii) CsOAc, DMF, rt; (iii) K_2CO_3, MeOH, rt.

The total synthesis of (±)-maritidine (**1**) disclosed herein is the first such synthesis, which does not utilize an oxidative phenol coupling to construct the quaternary center. An intramolecular Heck reaction followed by a dehydrogenation reaction provided the key intermediate spirocyclohexadienone (**11**). The synthesis of compounds related to maritidine and to other *Amaryllidaceae* alkaloids using this methodology is in progress.

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Supporting Information Available: Detailed experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Replacement of TlOAc by pentamethylpiperidine (PMP) or by a PMP and ^{n}Bu_4NOAc mixture afforded the expected tricyclic compound **9** but in low yields of 15 and 20%, respectively. When the reaction was performed in toluene, **9** was isolated in a lower yield (23%).

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