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IMDA-Radical Cyclization Approach to (+)-Himbacine

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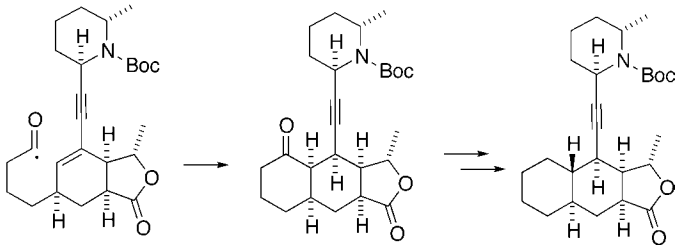
ABSTRACT



A formal total synthesis of the selective muscarinic receptor antagonist himbacine is presented. Key C–C bond-forming steps include an intramolecular Diels–Alder reaction, Stille coupling reactions, and a *6-exo-trig* acyl radical cyclization to a conjugated enyne. An unexpected secondary alcohol to chloride conversion is witnessed during attempted thionocarbonate formation.

Himbacine (**1**) (Figure 1) is an alkaloid extracted from *Galbulimima baccata*, a tree found in Northern Australia and Papua New Guinea.[1] Himbacine exhibits strong, selective binding to muscarinic receptors of the M_2 subtype,[2] a property that has potential medicinal applications.[3] The unique architecture of *Galbulimima* alkaloids, coupled with himbacine's promising biological activity, has provoked the synthetic efforts of several groups.[4−8] These approaches have delivered many analogues of himbacine for biological evaluation.[9] To date, however, no analogue has been reported with both higher potency and M_2-selectivity than himbacine. In efforts toward this end, we recently described concise syntheses of 4,4a-didehydrohimbacine **6** and *N*-methyl-4,-4a-didehydrohimandravine.[10] Whereas this approach allowed

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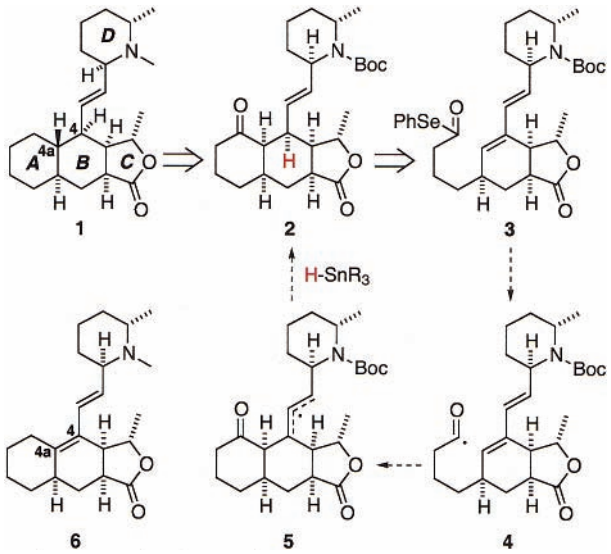


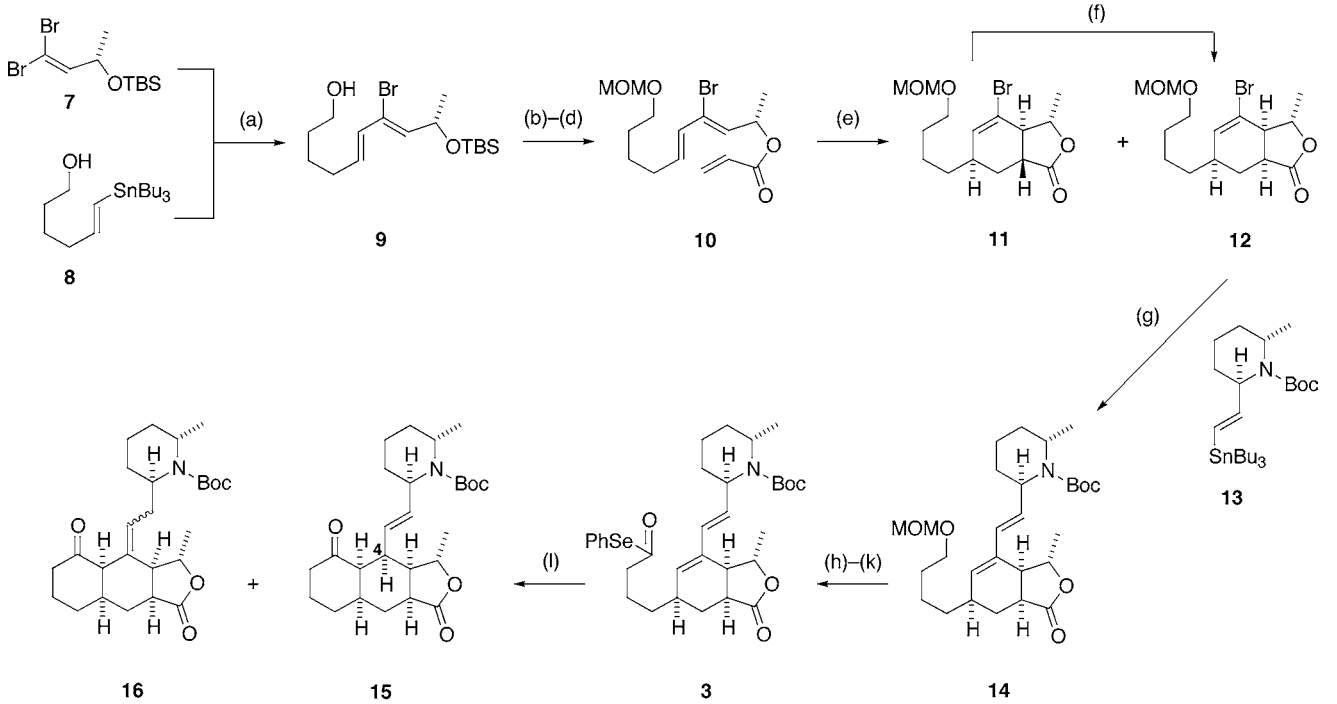
Figure 1. Intramolecular Diels−Alder/radical cyclization approach to himbacine.

rapid access to himbacine analogues, it is not amenable to the preparation of the natural product since a stereo- and regiocontrolled anti-1,2-addition of hydrogen to the more substituted alkene moiety of a conjugated diene would be necessary (i.e., **6** → **1**). Herein we report a total synthesis of himbacine that circumvents this problem.

The essence of this new approach is the utilization of the alkene moiety generated by the IMDA reaction as the site for intramolecular radical addition (Figure 1). Thus, an IMDA reaction on a [3]dendralene,[11] or a synthetic equivalent thereof, would generate the B/C bicyclic lactone **3**. A subsequent *6-exo-trig* acyl radical addition[12] to the resulting semicyclic diene would install the A ring of **2**. The requisite stereochemistry at C4 would be obtained by hydrogen atom delivery to the convex face of **5**. An epimerization at C4a and functional group interconversions would complete the synthesis.

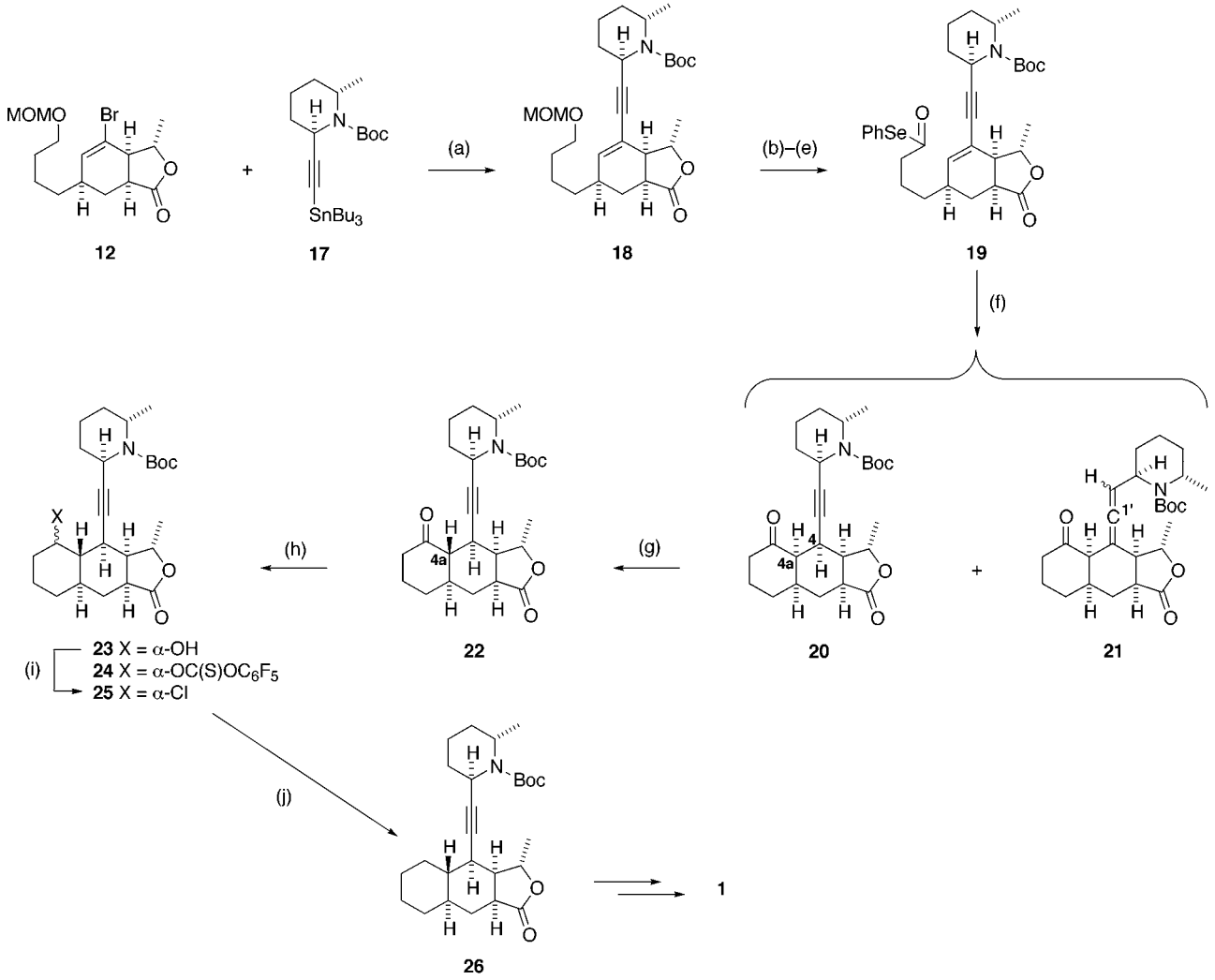
Selenoate ester **3** was prepared to investigate this proposal (Scheme 1). The synthesis of **3** begins with a Stille coupling between (*S*)-lactic acid-derived dibromoalkene **7**[13] and (*E*)-vinylstannane **8**,[14] which proceeded smoothly to give the (*Z*)-bromodiene **9** in high selectivity.[15] Protection of the primary alcohol as the MOM ether followed by desilylation and esterification with acryloyl chloride gave Diels−Alder precursor **10**. Bromopentadienyl acrylate **10** underwent an IMDA reaction in refluxing chlorobenzene over 6 days at ambient pressure to afford two cycloadducts **11** and **12** in

Scheme 1. Synthesis and Cyclization of Diene-Appended Radical Precursor **3**[a]



[a] Reaction conditions: (a) dibromide **7** (1.00 equiv), vinylstannane **8** (1.05 equiv), Pd_2dba_3 (0.0125 equiv), $AsPh_3$ (0.10 equiv), THF, 50 °C, 20 h, 72%; (b) MOM-Cl (5.0 equiv), *i*-Pr_2NEt (5.0 equiv), DMAP (0.1 equiv), CH_2Cl_2, 0 °C to rt, 3 h, 96%; (c) TBAF (1.5 equiv), THF, 0 °C to rt, 30 min, 94%; (d) CH_2═CHCOCl (1.5 equiv), Et_3N (2.1 equiv), CH_2Cl_2, 0 °C, 1 h, 91%; (e) PhCl ($[\mathbf{10}]_{initial}$ = 10 mM), BHT (0.05 equiv), reflux, 140 h, 75%, **11**:**12** = 84:16; (f) DBU (1.1 equiv), CH_2Cl_2, reflux, 17 h, 99%; (g) vinylstannane **13** (1.5 equiv), $Pd(PPh_3)_4$ (0.1 equiv), CuCl (5.0 equiv), LiCl (6.0 equiv), DMSO, 60 °C, 21 h, 86%; (h) PPTS (1.1 equiv), *t*-BuOH, reflux, 48 h; Boc_2O, CH_2Cl_2, rt, 17 h, 81%; (i) $(COCl)_2$ (2.1 equiv), DMSO (4.2 equiv), CH_2Cl_2, −78 °C, 1 h then Et_3N (10 equiv), 94%; (j) $NaClO_2$ (3 equiv), NaH_2PO_4 (3 equiv), 2-methyl-2-butene (8 equiv), THF/*t*-BuOH/H_2O (3:3:1), rt, 1 h, 93%; (k) Ph_2Se_2 (2 equiv), *n*-Bu_3P (2 equiv), DMF, rt, 18 h, 60%; (l) Ph_3SnH (1.5 equiv), Et_3B (1.2 equiv), air, PhH, reflux, 2 h, 65%, **15**:**16** = 20:80; **16*E***:**16*Z*** = 40:60.

Scheme 2. Synthesis and Cyclization of Enyne-Appended Radical Precursor **19**[a]



[a] Reaction conditions: (a) bromoalkene **12** (1.0 equiv), alkynylstannane **17** (1.5 equiv), $Pd(PPh_3)_4$ (0.1 equiv), CuCl (5.0 equiv), LiCl (6.0 equiv), DMSO, 60 °C, 21 h, 85%; (b) PPTS (1.1 equiv), *t*-BuOH, reflux, 48 h; Boc_2O, CH_2Cl_2, rt, 17 h, 75%; (c) $(COCl)_2$ (2.1 equiv), DMSO (4.2 equiv), CH_2Cl_2, −78 °C, 1 h then Et_3N (10 equiv), 95%; (d) $NaClO_2$ (3 equiv), NaH_2PO_4 (3 equiv), 2-methyl-2-butene (8 equiv), THF/*t*-BuOH/H_2O (3:3:1), rt, 1 h, 94%; (e) Ph_2Se_2 (2 equiv), *n*-Bu_3P (2 equiv), DMF, rt, 18 h, 76%; (f) Bu_3SnH (1.5 equiv), AIBN (0.1 equiv), PhH, reflux, 18 h, 90%, **20**:**21** = 48:52; (**21** C1′*S*:*R* = 50:50); (g) DBU (1.1 equiv), CH_2Cl_2, reflux, 7 h, 94%; (h) $NaBH_4$ (1.4 equiv), $CeCl_3 \cdot 7H_2O$ (1 equiv), MeOH, −78 °C, 4 h, 97% (α-OH:β-OH = 77:23); (i) $C_6F_5OC(S)Cl$ (9 equiv), DMAP (10 equiv), CH_3CN, reflux, 20 h, 87%; (j) Bu_3SnH (5.1 equiv), AIBN (cat.), PhMe, reflux, 7 h, 82%.

an 84:16 ratio, a stereochemical outcome consistent with previous investigations conducted with related precursors.[16]

The desired cis-fused adduct **12** was obtained in essentially quantitative yield after exposure of the IMDA product mixture to DBU.

The (*E*)-vinylpiperidine side chain was installed in high yield using Corey's cuprous chloride-accelerated Stille coupling procedure[17] between **12** and known vinylstannane **13**.[10] To complete the sequence, the primary MOM ether **14** was transformed into the phenylselenoate ester **3** by deprotection,[18] Swern oxidation,[19] Pinnick oxidation,[20] and esteri-

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fication.[21] The *6-exo-trig* radical cyclization of selenoate ester **3** was examined with a range of radical mediators (Bu_3SnH, $(Me_3Si)_3SiH$, and Ph_3SnH) under a variety of different conditions. The most fruitful of these gave the desired product in isolated yields of only 13%. The *regioselectivity* of H-atom delivery to allyl radical **5** (Figure 1) was the problem, as evidenced by isolation of the more highly substituted alkene **16** as the major product. Indeed, the ratio of **15**:**16** was 1:4 at best. Nevertheless, the C4 epimer of **15** could not be detected, an encouraging result that demonstrated a high degree of stereocontrol during H atom delivery to the more substituted end of the allylic radical.

Since the yield of the desired product **15** could not be improved by either switching the radical mediator or modifying of the reaction conditions, an alternative approach was necessary. We reasoned that a conjugated enyne should solve the problem, since delocalized allenic/propargylic radicals appear to react almost exclusively at the propargylic site.[22] Thus, selenoate ester **19**, an alkynic congener of **3**, was prepared from bromoalkene **12** as shown in Scheme 2. Stille coupling between vinyl bromide **12** and alkynylstannane **17**[23] was best performed once again in the presence of cuprous chloride. The protected primary alcohol **18** was elaborated into the acyl selenide **19** in good yield through the four-step sequence described earlier. Intriguingly, the reductive *6-exo-trig* radical cyclization furnished a ca. 1:1 mixture of alkynic (**20**) and allenic (**21**) products under all conditions examined, the best isolated yields being obtained with Bu_3SnH in refluxing benzene. Once again, the desired C4 trapping product **20** was produced as a single diastereoisomer, whereas the two allenes **21** were produced in equal amounts. Evidently, the regiochemistry of H atom delivery to allenic/propargylic radicals is sensitive to substitution.

Epimerization at C4a (**20** → **22**) was accomplished in excellent yield with DBU. We planned to remove the ketone group by reduction to the alcohol and then Barton−McCombie deoxygenation via thionocarbonate **24**. Luche reduction of the ketone at low temperature gave the axial alcohol **23** in excellent yield with high stereoselectivity. No reaction occurred upon attempted thionocarbonate formation at ambient temperature. Under more forcing conditions, however, we were surprised to witness a very clean conversion to the axial *chloride* (**25**). To our knowledge, such a transformation is without precedent in the thionocarbonate series; related conversions have, however, been witnessed with xanthates.[24] Reductive dechlorination of **25** with Bu_3SnH completes the formal total synthesis of himbacine.[25] We wonder whether some previously reported "deoxygenations" via the Barton−McCombie method have instead involved the removal of chlorine.

In summary, a novel route to himbacine has been developed. The route has allowed access to new analogues of the natural product, compounds that should shed light on the structural requirements for optimal potency and selectivity with muscarinic receptors.

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Supporting Information Available: Experimental procedures and product characterization data for key steps (**10** → **11** + **12**, **3** → **15** + **16**, **19** → **20** + **21**, **23** → **25**) and ^1H and ^{13}C NMR spectra of advanced intermediates **15**, **16**, **20**−**22**, **25**, and **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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