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Synthesis of huperzine B through ring closing metathesis

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Abstract—Huperzine B and its analogues were obtained through ring closing metathesis of *N*-alkenyl amine to the corresponding tricyclic compounds.

Huperzine A (**1**) and B (**2**), isolated from the clubmoss *Huperzia serrata* (*Yhunb.*)[1] Trev. = *Lycopodium serratum Thunb*., are potent, selective, reversible inhibitors of acetylcholinesterase (AChE).[2] In comparison to huperzine A, huperzine B demonstrates a higher therapeutic index in accordance with its longer duration of action.[3] Numerous synthetic organic chemists have made extensive efforts towards synthesizing huperzine A and its analogues. Synthesis of racemic huperzine B was first reported by Bai and Wu in 1997 and also enantioselective synthesis of (−)-huperzine B was recently disclosed by Taber.[4] We decided to synthesize huperzine B and its analogues because of its scarcity in plant and particular biological activity (Fig. 1).

In our plan, the ring closing metathesis (RCM) of *N*-alkenylamine **9** was utilized to prepare huperzine B and its analogues. Intermediate **5** of compound **8** was derived from a ketal **4** of 1,4-cyclohexane dione by the established procedure. And in an effort to obtain ester **6**, **5** was further treated via a series of reactions, including the Wittig reaction, *Z*–*E* isomerization, and *exo*–*endo* isomerization (Scheme 1).[5]

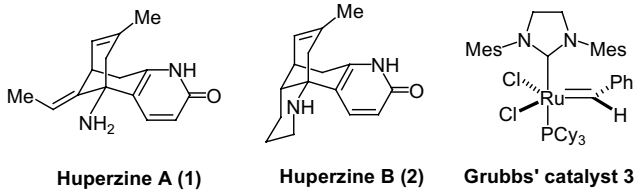
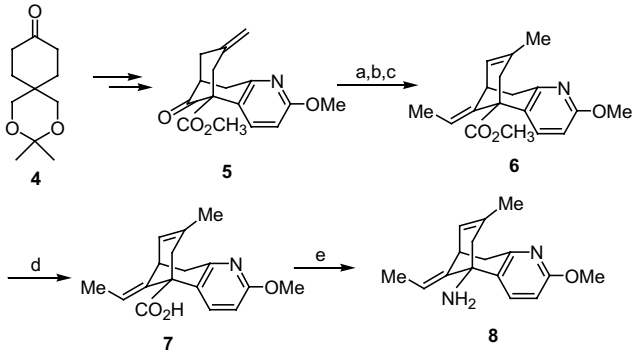


Figure 1.



Scheme 1. Reagents and conditions: (a) $Ph_3PCH_2CH_3Br$, *n*-BuLi, rt; (b) PhSH, toluene, 85 °C; (c) TfOH, dioxane, reflux; (d) NaOH, THF/MeOH, reflux; (e) $(PhO)_2P(O)N_3$, Et_3N, toluene, reflux: 8 N HCl reflux, 30 min or NaOH, rt, 2 h.

After the hydrolysis of **6** to carboxylic acid, carboxylic acid **7** was subjected to the Curtius rearrangement. The resulting isocyanate intermediate was treated with either HCl or NaOH to facilitate the production of amine **8** in 44% yield.

The alkenylation of **8** with alkenyl bromide and alkenyl iodide in the presence of NaH in DMF and HMPA, respectively, at 50 °C gave *N*-alkenyl products **9a**–**b** (58% and 64% yield) and **9c**–**d** (93% and 38% yield based on the recovered starting material).

Keywords: huperzine; ring closing metathesis; acetylcholinesterase (AChE) inhibitor.
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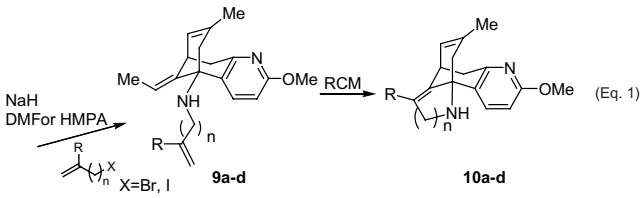

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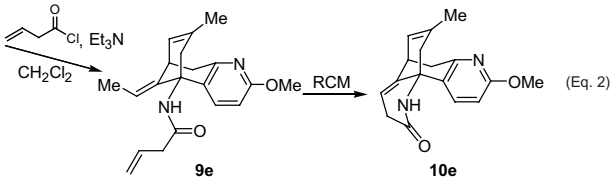
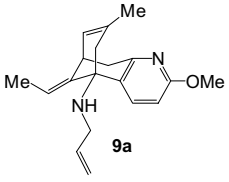
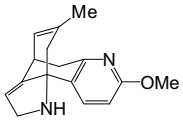
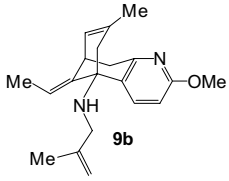
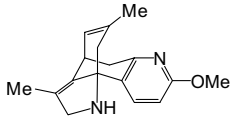
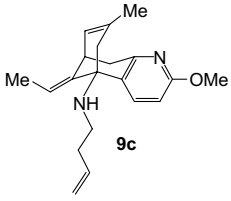
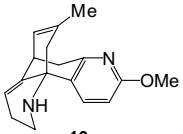
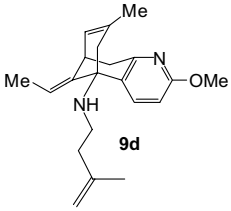
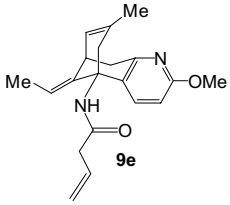
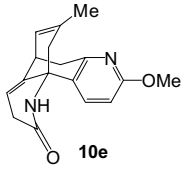


The RCM reaction of **9a**–**c** with Grubbs' second generation catalyst **3**[6] afforded cyclized products **10a**–**c** in moderate to good isolated yields (entries 1–3).[7] (Table 1) Homomethallyl **9d** did not render any cyclized product at all (entry 4). In addition, we applied this method to the synthesis of lactam **10e**. Treatment of **8** with 3-butenoyl chloride and triethylamine in dichloromethane at 0 °C gave amide **9e** in 97% yield. RCM reaction of **9e** provided cyclized product **10e** in lower yield (entry 5).

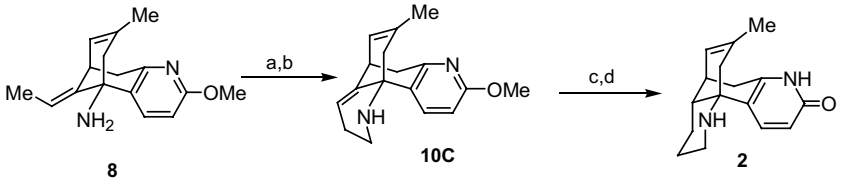
With the purpose of synthesis of huperzine B, we obtained homoallyl product **9c** on the reaction of amine **8** with 4-iodo-1-butene. Subsequent reactions of **9c** using the RCM reaction in the presence of Grubbs' catalyst, selective hydrogenation of double bond **10c** with Pd/C and final deprotection with TMSI furnished huperzine B (**2**) in 51% (three steps). The spectral data of **2** were identical to the results reported in the literature (Scheme 2).[4a]

In conclusion, we straightforwardly synthesized huperzine B and its analogues from amine **8** using RCM. The biological results of these compounds will be reported in the near future.

Table 1. Ring closing metathesis of *N*-alkenyl aminopyridine derivatives

Entry	Reactant	Reaction condition	Product (yield)[a]	
1	 **9a**	2 h, reflux	 **10a**	86
2	 **9b**	18 h, reflux	 **10b**	62
3	 **9c**	20 h, reflux	 **10c**	94
4	 **9d**	24 h, reflux	N.R. **10d**	
5	 **9e**	18 h, reflux	 **10e**	54

[a] All reactions were carried out in CH_2Cl_2 using 10% of catalyst.



Scheme 2. Reagents and conditions: (a) NaH, HMPA, 4-iodobutene, 50 °C; (b) **3**, CH_2Cl_2, reflux; (c) H_2, Pd/C, EtOH, rt; (d) TMSI, $CHCl_3$, reflux: MeOH, reflux.

Acknowledgements

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References and Notes

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7. Spectral data for **10c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, $J = 8.6$ Hz, 1H), 6.51 (d, $J = 8.6$ Hz, 1H), 5.61 (t, $J = 3.9$ Hz, 1H,), 5.38 (dd, $J = 3.8$, 1.3 Hz, 1H), 3.81 (s, 3H), 3.10 (t, $J = 4.8$ Hz, 1H), 3.02 (dd, $J = 16.8$, 5.5 Hz, 1H), 2.97–2.92 (m, 1H), 2.86 (t, $J = 4.8$ Hz, 1H), 2.82 (d, $J = 19.8$ Hz, 1H), 2.53 (d, $J = 16.5$ Hz, 1H), 1.97–1.92 (m, 3H), 1.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6, 153.3, 140.2, 135.9, 133.1, 132.3, 125.2, 115.8, 108.5, 53.9, 53.3, 47.9, 41.7, 40.3, 39.6, 26.4, 22.8; MS (m/z, rel int): 268 (100), 253 (92), 211, 154, 43.