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# A stereoselective formal total synthesis of (+)-hyperaspine via a tandem aza-Michael reaction☆

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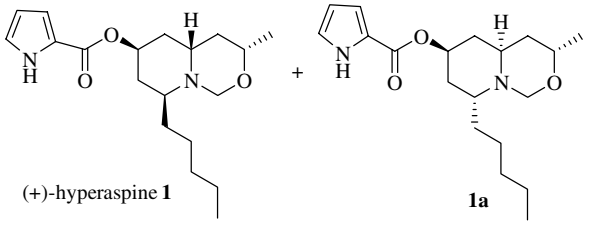
**Abstract**—A stereoselective formal total synthesis of (+)-hyperaspine via a tandem aza-Michael reaction as the key step in good yield is reported.


Hyperaspine **1**, belongs to the class of ladybird alkaloids, isolated from *Hyperaspia campestris* possessing a unique 3-oxaquinolizidine skeleton.[1] These structural features coupled with an interesting activity profile have prompted synthetic efforts toward **1**.[2] Ma and Zhu[2a] synthesized (+)-hyperaspine **1** through hydrogenation of a δ-hydroxy-β-ketoester-derived enamine to achieve the *syn* chiral amino alcohol, which was later extrapolated to the target compound. Subsequently, Braekman and co-workers[2b] achieved the total synthesis and established the absolute configuration of **1** starting from a protected piperidin-4-one. More recently, Commins and Sahn[2c] accomplished the total synthesis of **1** by the addition of a metalloenolate to a chiral, non-racemic 1-acylpyridinium salt. We recently embarked on a program[3] toward the synthesis of piperidine-containing bio-active natural products, and in this connection, herein a formal total synthesis of (+)-hyperaspine **1** is reported, wherein a novel one-pot, double aza-Michael reaction is utilized as the key reaction for construction of the important piperidinone ring-skeleton.

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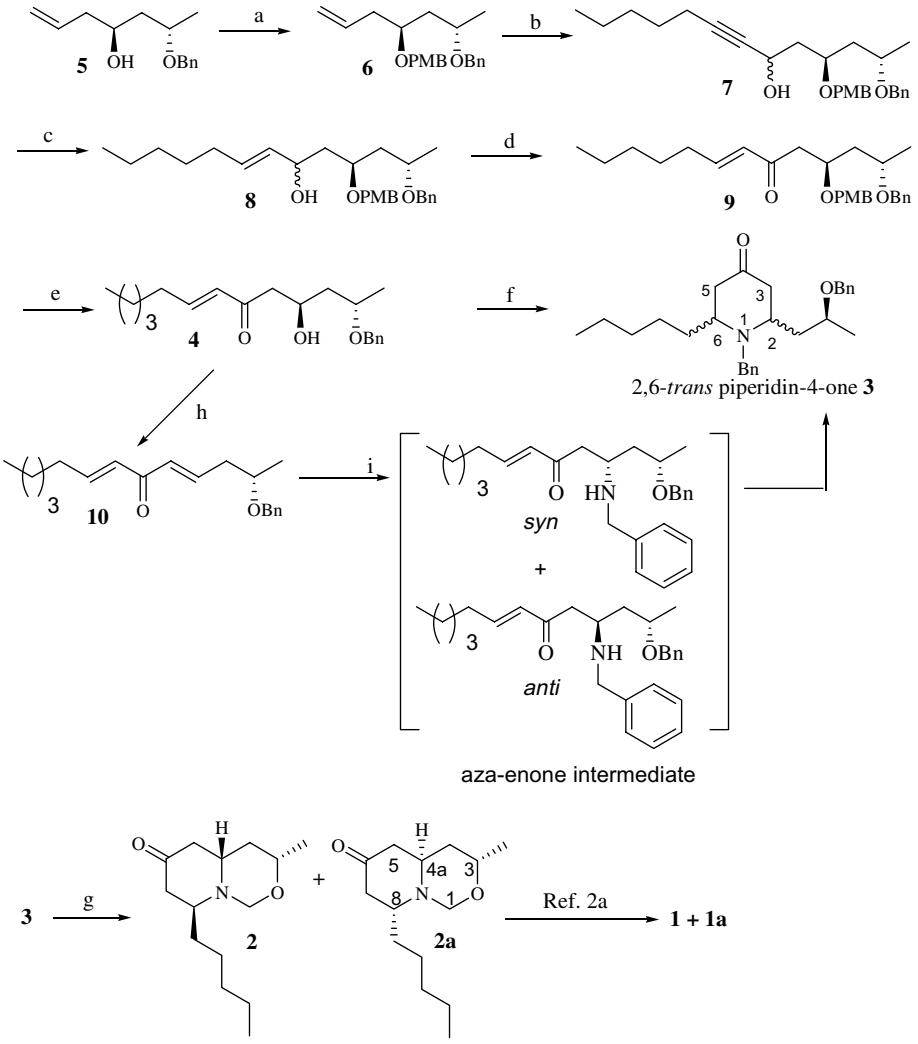
Initially, the strategy (Scheme 1) envisioned involved an intermolecular $S_N2$ reaction of a chiral mesylate, prepared from keto alcohol **4**, with benzylamine followed by conjugate addition to afford the piperidinone core skeleton **3**, which could subsequently be extrapolated to (+)-hyperaspine **1**.

As depicted in Scheme 1, the synthesis started with the known[4] homoallylic alcohol **5**. Thus, the hydroxyl of **5** was protected as its PMB ether **6** (NaH/PMBBr/DMF/rt), which on exposure to osmium tetraoxide ($OsO_4$/NMO/acetone:water/rt) mediated dihydroxylation and subsequent oxidative cleavage ($NaIO_4$/$CH_2Cl_2$/rt) of the ensuing diol resulted in an aldehyde, which without isolation was quenched with the acetylenic anion of 1-heptyne (*n*-BuLi/THF/−78 °C) to afford propargylic alcohol **7** (90% over three steps). Selective reduction of **7** with LAH in THF afforded allylic alcohol **8** (90%), which was oxidized (Dess–Martin periodinane/$CH_2Cl_2$/rt) to furnish ketone **9** (95%). Next, selective deprotection of the PMB ether (DDQ/$CH_2Cl_2$:water/rt) resulted in the keto alcohol **4** (95%).

Compound **4** was identified as an ideal substrate for $S_N2$ reaction of its corresponding mesylate with benzylamine followed by an intramolecular aza-Michael addition[5] to afford the piperidinone derivative **3**, which could eventually be transformed into 3-oxaquinolizidine **2**. Thus, mesylation of **4** ($MsCl/Et_3N/CH_2Cl_2$/−20 °C–rt) followed by in situ treatment with benzylamine resulted in **3** (90%) as an inseparable mixture of diastereomers. However, piperidinone **3** was resolved into two oxaquinolizidines **2** and **2a** upon cyclization (HCHO/MeOH/rt) in a 3:1 product ratio and 65% combined yield. The two products isolated were initially thought to be **2** and its




**Scheme 1.** Reagents and conditions: (a) NaH, DMF, PMB–Br, 0 °C–rt, 8 h, 85%; (b) (i) cat $O_SO_4$, NMO, acetone–water (4:1), 8 h, (ii) $NaIO_4$, $CH_2Cl_2$, rt, 2 h, (iii) 1-heptyne, *n*-BuLi, THF, −78 °C, 90% (over three steps); (c) LAH, THF, 0 °C–rt, 90%; (d) DMP, $CH_2Cl_2$, 0 °C–rt, 95%; (e) DDQ, $CH_2Cl_2$–$H_2O$ (9:1), 95%; (f) $Et_3N$, MsCl, DMAP (cat), −20 °C, 20 min, $BnNH_2$, 3 h, 90%; (g) (i) 10% Pd–C/$H_2$, MeOH, (ii) 37% aq HCHO, MeOH, 2 h, 65% (over two steps); (h) $Et_3N$, MsCl, DMAP (cat), $CH_2Cl_2$, −20 °C to 40 °C, 2 h; (i) $BnNH_2$, 3 h, rt.

C8-epimer.[2d] However, the spectral data of **2a** did not match with the reported values. For instance, the $^1H$ NMR spectrum of **2a** revealed H-1 at $\delta$ 4.59 and at $\delta$ 4.34 as doublets with $J_{gem} = 8.7$ Hz, while the C-8 epimer reportedly showed the same protons at $\delta$ 4.86 and $\delta$ 3.60 as doublets with $J_{gem} = 7.8$ Hz. The optical rotation value also differed {**2a**: $[\alpha]_D^{25}$ +15.53 (*c* 0.35, $CHCl_3$) whereas for the C-8 epimer:[2d] $[\alpha]_D^{25}$ −5.1 (*c* 1.1, $CHCl_3$)}. Both **2** and **2a** did not exhibit Bohlmann bands in the IR spectrum, thus inferring their existence as cis-fused ring conformers. Nevertheless the formation of **2a** needed to be rationalized, and could be logistically explained if a double aza-Michael addition of dienone **10** was envisaged as the intervening reaction to result initially in **3**, which was later converted into **2** and **2a**. This argument was indeed supported by the isolation of dienone **10** when the mesylation reaction was prolonged. Dienone **10** was synthesized by an alternate route,[6] double aza-Michael reaction of which produced identical results.

Further, the formation of **2**:**2a** in an isomeric ratio of 3:1 and the stereochemical preferential formation could be explained by considering[7] the fact that the first Michael reaction of dienone **10** with benzylamine was indeed a regio- and diastereoselective intermolecular aza-Michael reaction to afford an aza-enone intermediate (*syn* and *anti*, Fig. 1), which on second aza-Michael reaction (intramolecular) provided the 2,6-disubstituted-*trans*-piperidinones as exclusive products. While, the former regioselective Michael addition can possibly be explained by 10-membered H-bonding between the ketone and benzyl ether groups resulting in a diastereomeric ratio of 3:1 in favor of the requisite isomer; the exclusive *anti*-selectivity of the second aza-Michael reaction was mainly due to less prevalence of steric repulsions due to the substituents in the transition states (**B** and **D**, Fig. 1).[8]

The above analysis was found to be in complete agreement with the spectral data of **2** and **2a**.[9] Thus, the prod-

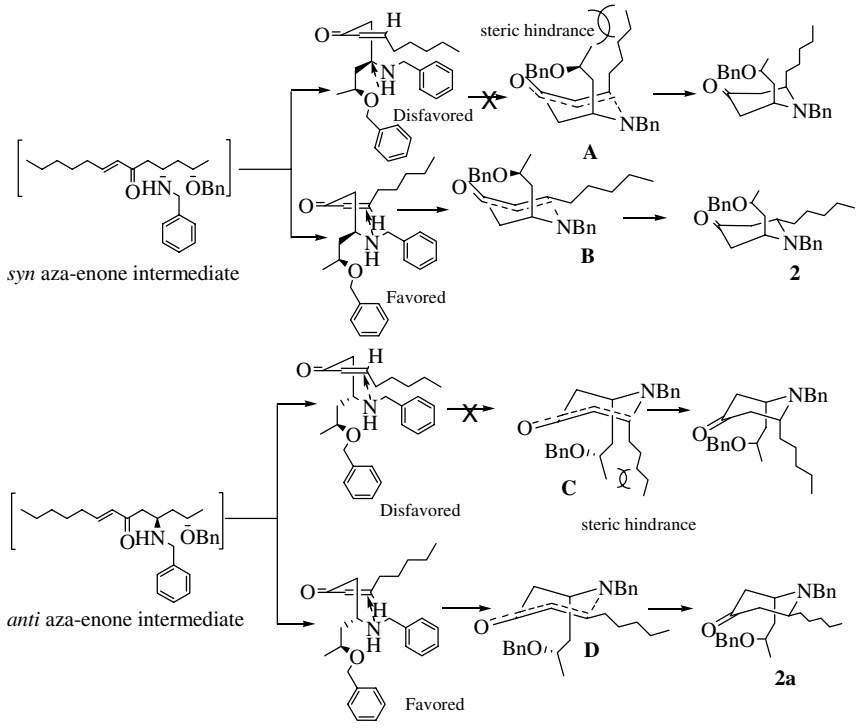



**Figure 1.** Stereoselectivity of the second aza-Michael addition.

uct profile was rationalized by the regio- and stereoselective aza-Michael addition of benzylamine at the β-carbon of the enone followed by stereospecific intramolecular aza-Michael addition. The physical and spectroscopic data of **2** were identical to the reported values. $[\alpha]_D^{25}$ +25.4 (*c* 0.75, $CHCl_3$); {lit.[2a] $[\alpha]_D^{25}$ +21.0 (*c* 0.67, $CHCl_3$). Hence, the synthesis of **2** reported herein constitutes a formal synthesis of (+)-hyperaspine **1**.

In conclusion, we have disclosed a concise and stereoselective formal total synthesis of (+)-hyperaspine **1** through a one-pot double aza-Michael reaction on a chiral enone intermediate. A highly stereocontrolled double aza-Michael reaction played a crucial role in minimizing the number of products. The synthesis takes advantage of the lone stereogenic center of the starting material in creating the additional chiral centers in a stereodefined fashion. A hitherto unreported diastereomeric 3-oxaquinolizidine **2a** was also synthesized through which an isomer of **1** could be realized. The strategy reported herein is general and can be adopted for the synthesis of similar piperidine-4-one systems.

## Acknowledgment

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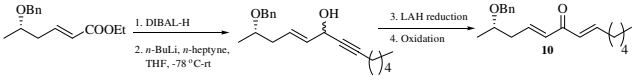
6. Compound **10** was independently synthesized from the known ester[2d] as follows:




7. It is logical to think that if the initial aza-Michael reaction were to occur on the β-carbon of the dienone nearer to the alkyl substituent the product ratio would have altered to 1:1 in favor of **2** and its C-8 epimer considering that the exclusive *anti*-selectivity of the second Michael reaction is still retained. Since the C-8 epimeric product was never observed, this argument was discounted.
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9. *Spectral data of selected compounds:* Compound **2a**: colorless oil; $[\alpha]_D^{25}$ +15.53 (*c* 0.35, $CHCl_3$); $^1H$ NMR (200 MHz,

$CDCl_3$): $\delta$ 4.59 (d, $J = 8.7$ Hz, 1H), 4.34 (d, $J = 8.7$ Hz, 1H), 3.95–3.77 (m, 1H), 3.62–3.47 (m, 1H), 3.27–3.11 (m, 1H), 2.63 (dd, $J = 13.8$, 10.1 Hz, 1H), 2.43 (dd, $J = 14.2$, 6.5 Hz, 1H), 2.22–2.09 (m, 2H), 1.75–1.15 (m, 13H), 0.88 (t, $J = 6.5$ Hz, 3H); FTIR (neat): 2941, 2854, 1715 $cm^{-1}$; MS ESI 240 ($M^+$+1). Compound **2**: colorless oil; $[\alpha]_D^{25}$ +25.4 (*c* 0.75, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 4.73 (d, $J = 10.5$ Hz, 1H), 4.24 (d, $J = 10.5$ Hz, 1H), 3.63 (m, 1H), 3.48 (m, 1H), 3.36 (m, 1H), 2.68 (ddd, $J = 14.0$, 6.4, 1.2 Hz, 1H), 2.48–2.26 (m, 2H), 2.16 (ddd, $J = 13.9$, 4.5, 1.8 Hz, 1H), 1.63–1.20 (m, 10H), 1.18 (d, $J = 6.4$ Hz, 3H), 0.88 (t, $J = 6.5$ Hz, 3H); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 14.0, 21.5, 22.5, 24.6, 30.8, 31.9, 35.7, 45.5, 46.9, 53.2, 56.3, 73.5, 81.1, 209.0; FTIR (neat): 2945, 2861, 1722, 1350, 1236, 1098 $cm^{-1}$; MS ESI 240 (M+1); Anal. Calcd for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.21; H, 10.51; N, 5.79. Compound **4**: colorless oil; $[\alpha]_D^{25}$ +10.7 (*c* 1.0, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.32–7.19 (m, 5H, Ar–H), 6.85–6.72 (m, 1H), 6.05 (d, $J = 15.8$ Hz, 1H), 4.59 (d, $J = 11.3$ Hz, 1H), 4.43 (d, $J = 11.3$ Hz, 1H), 4.33–4.24 (m, 1H), 3.89–3.79 (m, 1H), 2.63 (dd, $J = 7.9$, 3.7 Hz, 2H), 2.24–2.13 (m, 2H), 1.5 (dt, $J = 7.9$, 3.3 Hz, 2H), 1.33–1.22 (m, 9H), 0.90 (t, $J = 6.4$ Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 13.91, 19.65, 22.54, 27.64, 31.29, 32.44, 43.37, 46.35, 65.12, 70.82, 72.15, 127.54, 127.78, 128.35, 130.52, 138.80, 149.09, 201.04; IR (neat): 3400, 3050, 1710, 1605, 1120 $cm^{-1}$; LC–MS 341.3 $(M+Na)^+$; Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.27; H, 9.68.