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Stereocontrolled concise synthesis of (±)-halosaline through intramolecular C-H amination

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ABSTRACT

Total synthesis of 2-(2-hydroxyalkyl)-piperidine alkaloid (±)-halosaline is described from 7-octen-4-ol using a Rh-catalyzed chemo- and diastereo-selective intramolecular C—H amination of sulfamate ester, ring-closing metathesis, and S_N2 displacement reaction of the six-membered ring sulfamidate as the key steps.

C—H bond amination has emerged as an effective means for the synthesis of complex nitrogen-containing molecules. Following the early discoveries by Breslow and Gellman [1], Du Bois and co-workers revolutionized this domain of chemistry by developing protocols for practical, efficient, and predictable reactions for oxidative C—H amination [2]. In this regard, dirhodium (II) tetracarboxylate catalysts were shown to be particularly effective. Other catalysts such as ruthenium [3], manganese [4], silver [5], and iron [6] complexes have also been developed for this important reaction. Given the prevalence of nitrogen functionalities in biologically active molecules and the relative difficulty of incorporating nitrogen into molecular frameworks, C—H amination has found a unique place in total synthesis, examples of which include the preparation of (−)-tetrodotoxin [7], (+)-saxitoxin [8], manzacidins A and C [9], (−)-agelastatin A [10], and (−)-*N*-methylwelwitindolinone C isothiocyanate [11]. These works underscore the robustness of C—H amination for streamlining total synthesis.

Piperidine alkaloids are widely distributed in nature and found to exhibit a broad spectrum of biological activities [12]. In particular 2-(2-hydroxy substituted)-piperidine alkaloids (Fig. 1) have attracted considerable attention due to their potent biological activities such as memory-enhancing properties [13]. These alkaloids generally differ by the side chain and also stereochemistry of 1,3-aminoalcohols. Halosaline **1**, a representative 2-(2-hydroxy substituted)-piperidine alkaloid was isolated from *Haloxylon Salicornicum* [14]. Although there are several literature reports on the synthesis of halosaline [15], C—H amination strategy has never been explored. Here we wish to report our own results.

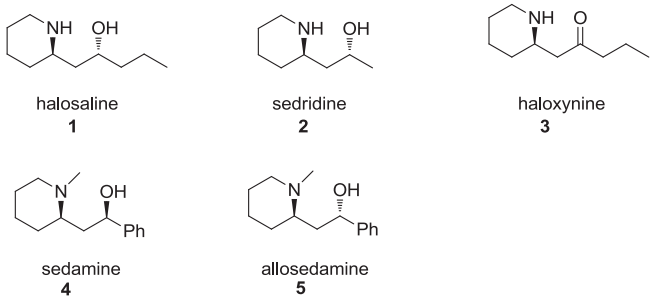

Fig. 1. 2-(2-Hydroxy substituted)-piperidine alkaloids.

As illustrated in Scheme 1, we envisioned that the *anti* 1,3-aminoalcohol unit of halosaline **1** could be obtained from *syn* sulfamidate **6** through a S_N2 displacement at the final stage. The piperidine ring of **6** was envisioned to arise from two sequences involving hydrogenation of the olefin **7** and formation of the double bond through a ring-closing metathesis reaction. Thus, diene **8** would be a logical precursor to **7**. Further analysis revealed that diene **8** could be derived from an *N*-alkylation of sulfamidate **9**. Six-membered ring sulfamidate **9** is a key intermediate in our design because we could exploit C—H amination in its preparation.

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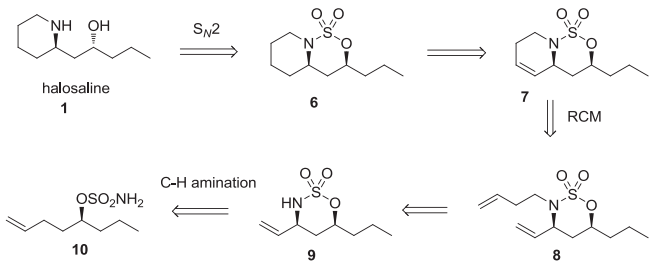

Scheme 1. Retrosynthetic analysis of (±)-halosaline.

Similar to what has been shown in the literature [6a], we hypothesized that allylic C—H bond in sulfamate ester **10** could be differentiated and selectively functionalized by sulfamate insertion. Furthermore, this C—H amination would demonstrate excellent 1,3-diastereoselective induction due to the cyclization event proceeding through a chairlike transition state [2b]. In this way, the stereogenic amine center from remote alcohol group could be easily established. Notably, this C—H amination strategy is suited ideally for the preparation of halosaline **1** given the effectiveness of the stereocontrol in the sulfamate ester cyclization with sulfamidate ring opening protocol.

Our synthetic pathway towards (±)-halosaline **1** is outlined in Scheme 2. Reduction of known 7-octen-4-one **11** with $NaBH_4$ gave 7-octen-4-ol **12**, which was further converted to sulfamate ester **10** employing sulfamoyl chloride that was generated from $ClSO_2NCO$ and formic acid. The sulfamate ester **10** reacted rapidly at 40 °C with $PhI(OAc)_2$, MgO, and 10 mol % $Rh_2(OAc)_4$ to afford the corresponding six-membered ring insertion product **9** through a chemo- and diastereo-selective allylic C—H insertion. With *syn* sulfamidate **9** in hand, the stage was set to install the piperidine ring. To this end, *N*-alkylation of sulfamidate **9** with NaH and 4-bromobut-1-ene provided diene **8** in 77% yield. Subsequent ring-closing metathesis of diene **8** with Grubbs II catalyst delivered bicycle **7** in 96% yield. Catalytic hydrogenation of the alkene **7** afforded piperidine **6** in nearly quantitative yield. Ring-opening of sulfamidate **6** with nucleophilic acetate anion at 80 °C underwent smoothly to afford piperidine **13**. The resulting acetate group of crude **13** was cleaved with potassium carbonate, providing (±)-halosaline **1** in moderate yield for two steps. Alternatively, treatment of piperidine **13** with Ts_2O gave **14**. Compound **14** was much more easily purified than piperidine **13** and could be obtained in high purity. After removal of the acetate, the same compound **15** reported by Blechert could be delivered [15c]. Cleavage of the tosyl-group of **15** was achieved using Na/Hg in methanolic phosphate buffer according to Blechert's procedure, providing (±)-halosaline **1**.

Considering water might be a better nucleophile in the ring-opening of heterocycle **6** because its product would be halosaline **1** directly, we followed the literature procedure by using vigorous conditions (4 N HCl, dioxane, 140 °C).[16] Although the S_N2 displacement reaction of sulfamidate **6** indeed took place, the product was turned out to be a chloride **16** whose structure was unanimously assigned by X-ray crystallographic analysis of its derivative **17**. In this case, not surprisingly, chlorine atom from HCl acts a nucleophile.

In conclusion, we have disclosed a short diastereoselective total synthesis of 2-(2-hydroxyalkyl)-piperidine alkaloid (±)-halosaline **1**. The highlights include a Rh-catalyzed chemo- and diastereoselective intramolecular C—H amination of sulfamate ester, ring-closing metathesis, and S_N2 displacement reaction of the six-membered ring sulfamidate. It is noteworthy that the strategy described herein would be applicable to its asymmetric version because enantioselective preparation of alcohols such as **12** is not difficult [17].

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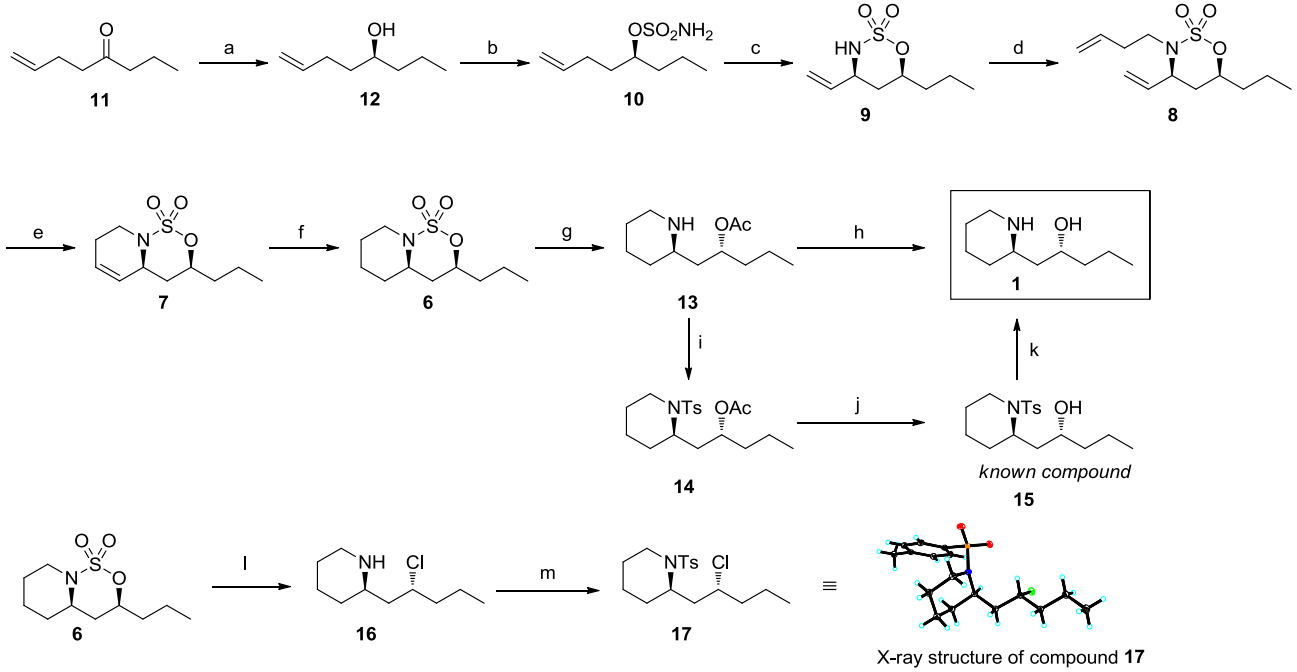

Scheme 2. Reagents and conditions. (a) $NaBH_4$, MeOH, 92%; (b) $ClSO_2NCO$, HCOOH, Et_3N, DCM, 80%; (c) $Rh_2(OAc)_4$, MgO, $PhI(OAc)_2$, DCM, 40 °C, 63%; (d) 4-bromobut-1-ene, NaH, DMF, 77%; (e) Grubbs II catalyst, DCM, 40 °C, 96%; (f) Pd/C, MeOH, 97%; (g) KOAc, DMF, 80 °C; (h) K_2CO_3, MeOH, 40%, 2 steps; (i) Ts_2O, Et_3N, DMAP, DCM, 35%, 2 steps; (j) K_2CO_3, MeOH, 80%; (k) Na_2HPO_4, Na/Hg (10%), MeOH, reflux, ref 15c; (l) Dioxane, 4 N HCl, 140 °C; (m) TsCl, Et_3N, DCM, 45%, 2 steps.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.05.068.

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