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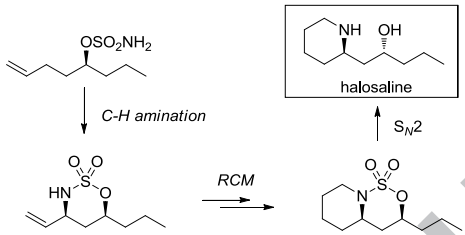

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Stereocontrolled concise synthesis of (±)-halosaline through intramolecular C-H amination

Chun-Yan Meng[a,b], Xiao Liang[a], Hongbin Zhang[b], Kun Wei[a,*] and Yu-Rong Yang[a,*]

[a]*State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650201, China*
[b]*Key Laboratory of Medicinal Chemistry for Natural Resources (Yunnan University), Ministry of Education, School of Chemical Science and Technology, Yunnan University, Kunming 650091, China*

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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.

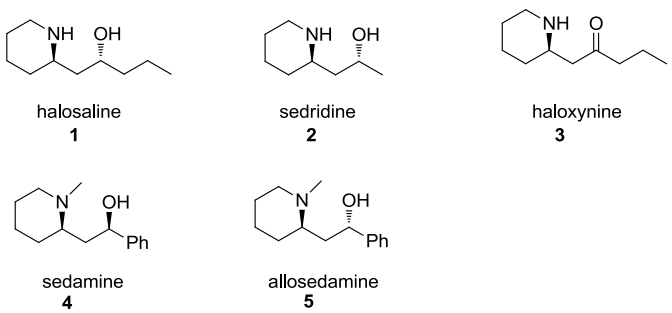
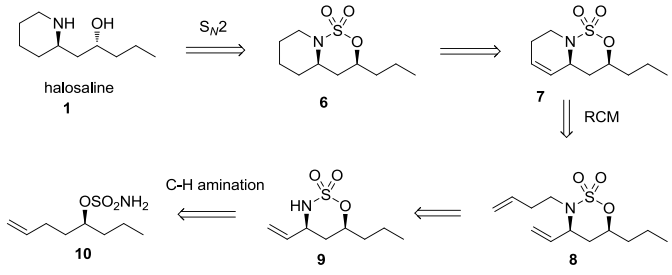


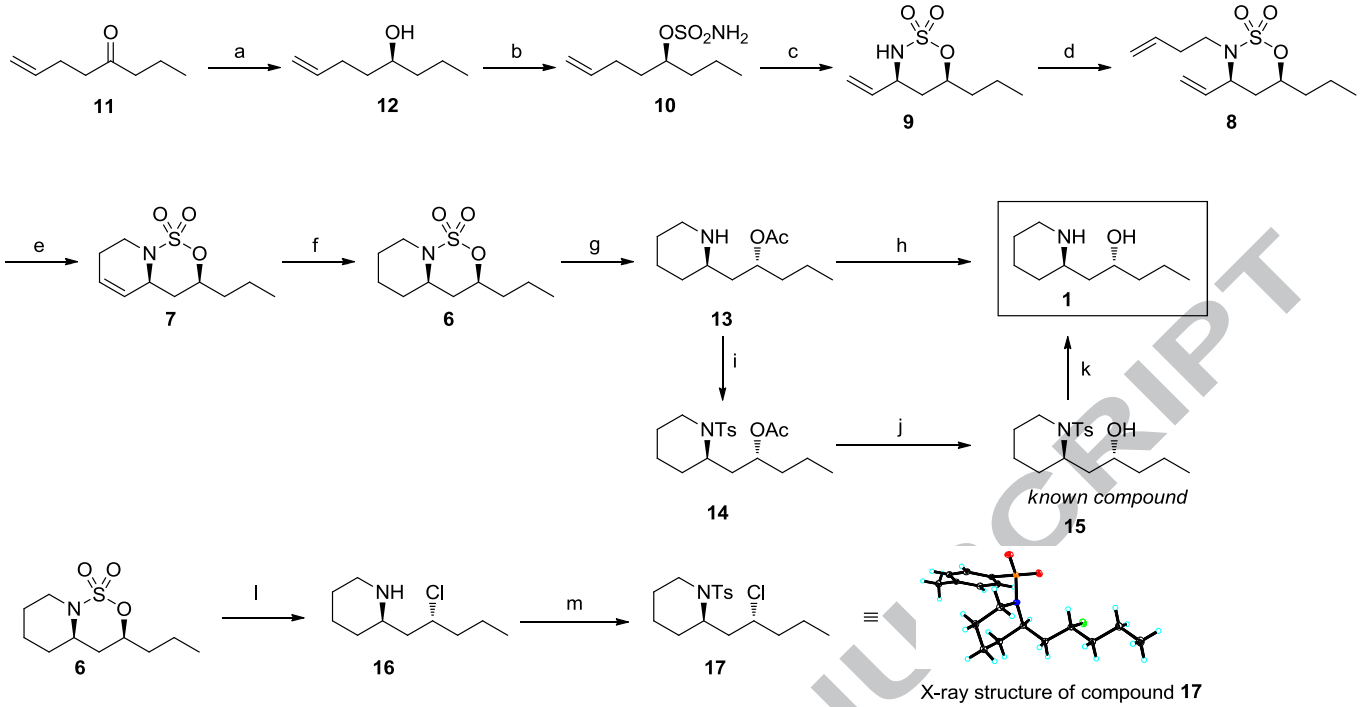
Figure 1. 2-(2-Hydroxy substituted)-piperidine alkaloids

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 (Figure 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.



Scheme 1. Retrosynthetic analysis of (±)-halosaline

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 analy



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, 4N HCl, 140 °C; (m) TsCl, Et_3N, DCM, 45%, 2 steps.

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. 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 (4N 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 diastereo-selective 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]

Acknowledgments

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at

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