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Formal synthesis of (±)-sedamine through gold(I)-catalyzed intramolecular dehydrative amination of sulfamate esters tethered to allylic alcohols

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ABSTRACT

A concise formal synthesis of (±)-sedamine has been accomplished. The synthesis is straightforward and demonstrates high efficiency. Key steps involve gold(I)-catalyzed cyclization of sulfamate esters tethered to allylic alcohols, sulfamate *N*-alkylation, and ring-closing metathesis.

Introduction

1,3-Aminoalcohols [1] are frequently found in many bioactive synthetic and natural products, and often exist as key structural motifs in complex bioactive molecules. Particularly, when they are integrated as a part of piperidine structure, they form important classes of alkaloids, 2-(2-hydroxy substituted) piperidine alkaloids [2]. The 2-(2-hydroxy substituted) piperidine alkaloids vary structurally in their 2-alkyl side chains, *N*-substitutions, and stereochemistry of 1,3-aminoalcohols as shown in Fig. 1. These alkaloids also exhibit a wide spectrum of biological activities, which have attracted considerable attention of medicinal chemists for several decades.

Sedamine and sedridine, two representative 2-(2-hydroxy substituted) piperidine alkaloids, were first isolated from *Sedum acre* [3] and were also obtained later from several other *Sedum* species. Both levorotatory and dextrorotatory sedamines were found in all *Sedum* species [4]. Pharmacologically, the sedamines offer memory-enhancing properties for treatment of cognitive disorders [5]. These alkaloids can be isolated in small quantities from natural sources, and thus much effort has been devoted to the syntheses of sedamine, either as a racemate [6] or as a single enantiomer [7] (Scheme 1).

Although several studies in the literature report on the synthesis of sedamine, the synthesis of 1,3-aminoalcohol moiety is always an issue. Despite previously reported elegant works [8], there is an increasing demand to develop a general and mild method to synthesize the 1,3-aminoalcohol scaffold. To address this issue, we explored a dehydrative amination strategy for the synthesis of 1,3-aminoalcohols (Scheme 2). In our previous work, we developed gold(I)-catalyzed intramolecular dehydrative amination of sulfamate esters tethered to allylic alcohols **A** leading to 1,3-cyclic sulfamidate **B**, which are important synthetic intermediates that are broadly exploited for the synthesis of various functionalized amines [9]. The 1,3-cyclic sulfamidates are as reactive as activated azetidines [10]. Nucleophiles generally attack at the *O*-bearing carbon center in an S_N2 manner to form an *N*-sulfate intermediate [11], which can be rapidly hydrolyzed under acidic conditions to the final 1,3-aminoalcohol **C** (Scheme 2). Based on this strategy, we herein report the formal synthesis of (±)-sedamine through gold(I)-catalyzed intramolecular dehydrative amination of sulfamate esters tethered to allylic alcohols.

Our retrosynthetic analysis is briefly illustrated in Scheme 3. The primary target molecule is the *N*-Boc-2-(2-hydroxyethyl) piperidine (**2**) because the compound **2** was already transformed into (±)-sedamine in three steps [12]. We envisioned that the key synthetic intermediate **2** might be constructed by the cleavage of cyclic sulfamate ring and *N*-Boc protection. The bicyclic sulfamate **3** could be prepared via a ring-closing metathesis and following

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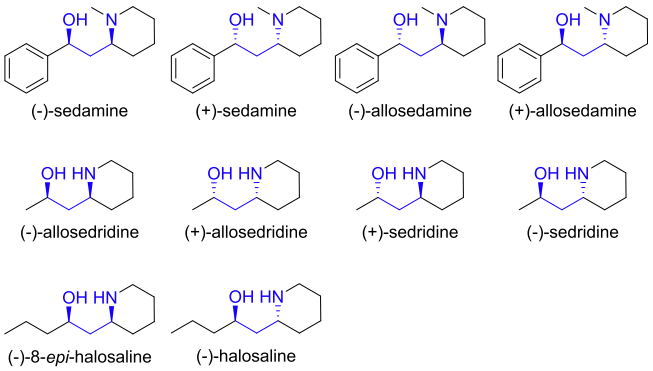
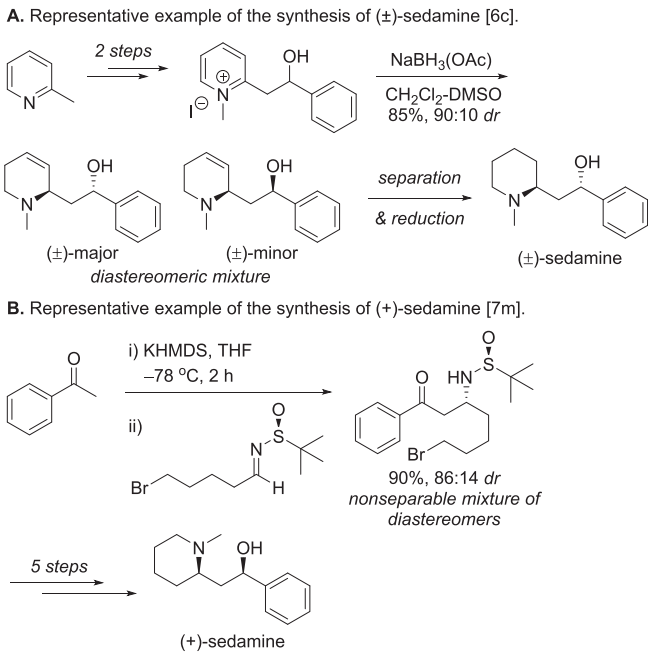
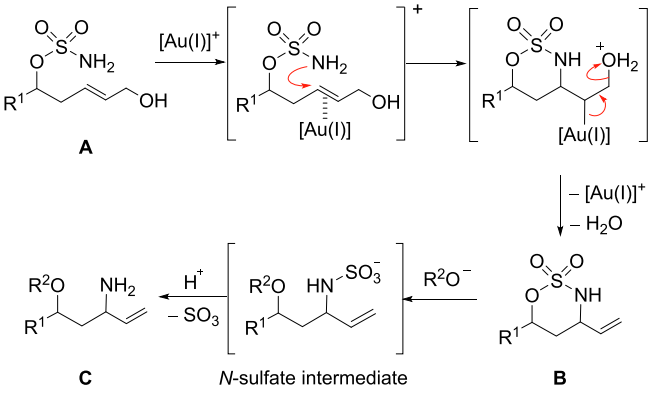


Fig. 1. 2-(2-Hydroxy substituted) piperidine alkaloids.

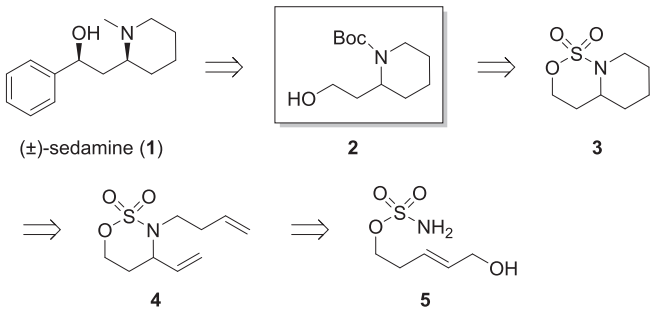


Scheme 1. Representative examples of the synthesis of sedamine.



Scheme 2. Strategies for the synthesis of 1,3-aminoalcohols.

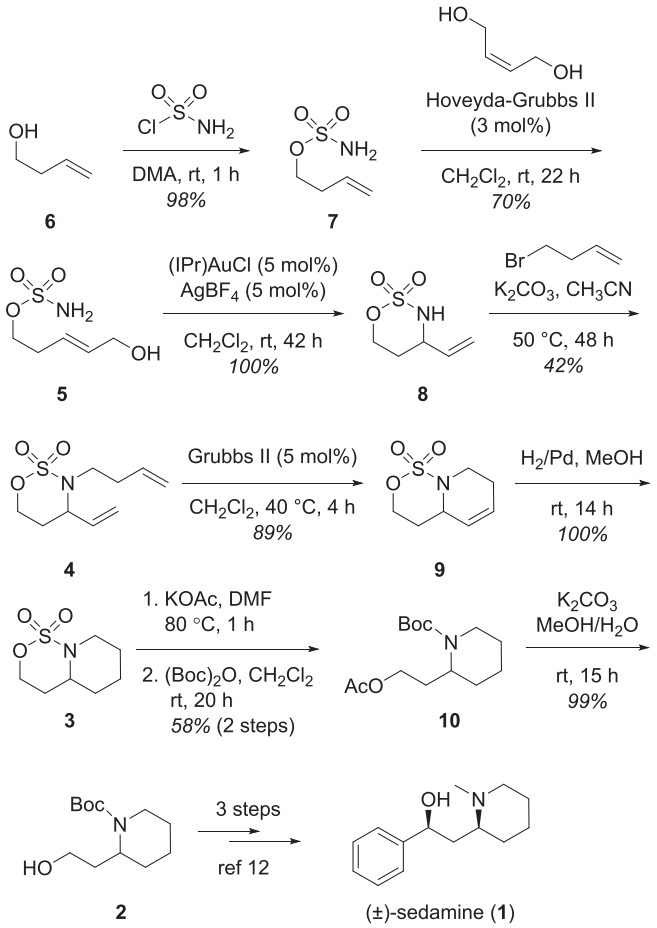
hydrogenation from diene **4**, which was derived from the sulfamate ester **5** tethered to allylic alcohol via gold(I)-catalyzed dehydrative amination and *N*-alkylation.



Scheme 3. Retrosynthetic analysis of (±)-sedamine.

Results and discussion

The efficient synthesis of the primary target molecule **2** began with commercially available but-3-en-1-ol (**6**) (Scheme 4). The sulfamoylation of alcohol **6** to sulfamate ester **7** was performed using sulfamoyl chloride according to the precedent literature [13], which cleanly provided the desired product at room temperature in 98% yield. The allyl alcohol tether of **5** was installed via a cross metathesis reaction using (*Z*)-but-2-ene-1,4-diol in the presence of 3 mol% of Hoveyda-Grubbs 2nd generation catalyst. Next, we carried out gold(I)-catalyzed cyclization of sulfamate ester **5** tethered to allylic alcohol in the presence of 5 mol% of (IPr)AuCl and 5 mol% of $AgBF_4$, which gave the desired 1,3-cyclic sulfamidates **8** in a quantitative yield after 42 h. The reaction was very mild and proceeded cleanly at room temperature. This method was



Scheme 4. Formal synthesis of (±)-sedamine alkaloid.

recently developed in our group [9] and the optimized conditions using (IPr)AuCl/$AgBF_4$ combination exhibited a broad substrate scope, including a seven-membered ring formation. It turns out that this established method also works well for the formal synthesis of (±)-sedamine. The resulting vinyl motif of **8** was used as an olefin partner for ring-closing olefin metathesis. To incorporate the other olefin partner, *N*-alkylation of 1,3-cyclic sulfamidate **8** was achieved with K_2CO_3 and 4-bromobut-1-ene. Following the ring-closing metathesis of diene **4** with 5 mol% of Grubbs 2nd generation catalyst furnished unsaturated piperidine **9** in 89% yield. The hydrogenation using H_2/Pd condition afforded bicyclic sulfamidate **3** in nearly quantitative yield. The ring cleavage of 1,3-cyclic sulfamidate of **3** using potassium acetate nucleophile and subsequent Boc protection allowed the ring-opened 1,3-amino acetate **10** in 58% yield in two steps. Finally, the acetate was converted to 2-(2-hydroxy substituted) piperidine **2** under basic hydrolysis conditions.

Conclusion

In conclusion, an efficient formal synthesis of 2-(2-hydroxyalkyl)-piperidine alkaloid (±)-sedamine has been achieved. Notable features include a gold(I)-catalyzed intramolecular dehydrative amination of sulfamate ester tethered to allyl alcohol, ring-closing metathesis, and sulfamidate ring cleavage in an S_N2 manner. It is noteworthy that this strategy is applicable to the synthesis of other 2-(2-hydroxyalkyl)-piperidine alkaloids.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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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.2021.153024.

References

[1] (a) For examples of bioactive 1,3-amino alcohols, see: P.A. Jacobi, S. Murphree, F. Rupprecht, W. Zheng J. Org. Chem. 61 (1996) 2413;
(b) F. Benedetti, S. Norbedo, Chem. Commun. (2001) 203;
(c) H.L. Sham, C. Zhao, L. Li, D.A. Betebenner, A. Saldivar, S. Vasavanonda, D.J. Kempf, J.J. Plattner, D.W. Norbeck, Bioorg. Med. Chem. Lett. 12 (2002) 3101;
(d) Z. Shi, B.A. Harrison, G.L. Verdine, Org. Lett. 5 (2003) 633;
(e) B. Raju, K. Mortell, S. Anandan, H. O'Dowd, H. Gao, M. Gomez, C. Hackbarth, C. Wu, W. Wang, Z. Yuan, R. White, J. Trias, D.V. Patel, Bioorg. Med. Chem. Lett. 13 (2003) 2413.
[2] (a) For examples of 2-(2-hydroxy substituted) piperidine alkaloids, see: A. Bisai, V.K. Singh Tetrahedron. Lett. 48 (2007) 1907;
(b) E. Bonandi, P. Marzullo, F. Foschi, D. Perdicchia, L.L. Presti, M. Sironi, S. Pieraccini, G. Gambacorta, J. Saupe, L. Dalla Via, D. Passarella, Eur. J. Org. Chem. (2019) 4013;
(c) E. Bonandi, G. Tedesco, D. Perdicchia, D. Passarella, Molecules 25 (2020) 1057.
[3] (a) L. Marion, Can. J. Res. 23B (1945) 165;
(b) L. Marion, R. Lavigne, L. Lemay, Can. J. Chem. 29 (1951) 347;
(c) B. Franck, Chem. Ber. 91 (1958) 2803;
(d) B. Franck, Chem. Ber. 93 (1960) 2360;
(e) G. Fodor, D. Butruille, S.C. Huber, F. Letourneau, Tetrahedron 27 (1971) 2055, and references cited therein.
[4] J.H. Kim, H.T. Hart, J.F. Stevens, Phytochemistry 41 (1996) 1319.
[5] O. Meth-Cohn, C.-Y. Yu, P. Lestage, M.-C. Lebrun, D.-H. Caignard, P. Renard, Eur. Pat. 1,050,531, 2000.
[6] (a) For selected syntheses of (±)-sedamine, see: R.W. Bates, K. Sa-Ei Tetrahedron 58 (2002) 5957;
(b) B.A.D. Neto, A.A.M. Lapis, A.B. Bernd, D. Russowsky, Tetrahedron 65 (2009) 2484;
(c) A. Boussonnière, T. Ranaivondrambola, J. Lebreton, M. Mathé-Allainmat, Synthesis (2010) 2456.
[7] (a) For selected syntheses of chiral sedamine, see: J. Cossy, C. Willis, V. Bellosta, S. BouzBouz J. Org. Chem. 67 (2002) 1982;
(b) F.-X. Felpin, J. Lebreton, J. Org. Chem. 67 (2002) 9192;
(c) M. Angoli, A. Barilli, G. Lesma, D. Passarella, S. Riva, A. Silvani, B. Danieli, J. Org. Chem. 68 (2003) 9525;
(d) N.S. Josephsohn, M.L. Snapper, A.H. Hoveyda, J. Am. Chem. Soc. 126 (2004) 3734;
(e) G. Zheng, L.P. Dwoskin, P.A. Crooks, J. Org. Chem. 69 (2004) 8514;
(f) R.W. Bates, J. Boonsombatb, Org. Biomol. Chem. 3 (2005) 520;
(g) J.S. Yadav, M.S. Reddy, P.P. Rao, A.R. Prasad, Tetrahedron Lett. 47 (2006) 4397;
(h) J.S. Yadav, M.S. Reddy, P.P. Rao, A.R. Prasad, Synthesis (2006) 4005;
(i) S. Fustero, D. Jiménez, J. Moscardó, S. Catalán, C.d. Pozo, Org. Lett. 9 (2007) 5283;
(j) T. Spangenberg, B. Breit, A. Mann, Org. Lett. 11 (2009) 261;
(k) S.G. Davies, A.M. Fletcher, P.M. Roberts, A.D. Smith, Tetrahedron 65 (2009) 10192;
(l) G. Satyalakshmi, K. Suneel, D.B. Shinde, B. Das, Tetrahedron: Asymmetry 22 (2011) 1000;
(m) A.A. Reddy, K.R. Prasad, J. Org. Chem. 82 (2017) 13488.
[8] (a) For selected syntheses of 1,3-aminoalcohols, see: H. Kohls, M. Anderson, J. Dickerhoff, K. Weisz, A. Córdova, P. Berglund, H. Brundiek, U.T. Bornscheuer, M. Höhne Adv. Synth. Catal. 357 (2015) 1808;
(b) P.A. Spreider, A.M. Haydl, M. Heinrich, B. Breit, Angew. Chem. Int. Ed. 55 (2016) 15569;
(c) R. Ma, J. Young, R. Promontorio, F.M. Dannheim, C.C. Pattillo, M.C. White, J. Am. Chem. Soc. 141 (2019) 9468.
[9] Y. Park, J.S. Lee, J.-S. Ryu, Adv. Synth. Catal. 363 (2021), https://doi.org/10.1002/adsc.202001330.
[10] J.F. Bower, J. Svenda, A.J. Williams, J.P. Charmant, R.M. Lawrence, P. Szeto, T. Gallagher, Org. Lett. 6 (2004) 4727.
[11] A. Avenoza, J.H. Busto, F. Corzana, G. Jiménez-Osés, J.M. Peregrina, Chem. Commun. (2004) 980.
[12] T.M. Shaikh, A. Sudalai, Eur. J. Org. Chem. (2010) 3437.
[13] R. Appel, G. Berger, Chem. Ber. 91 (1958) 1339.