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Communication

Concise Total Synthesis of Salimabromide

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ABSTRACT: We achieved a concise total synthesis of salimabromide by using a novel intramolecular radical cyclization to simultaneously construct the unique benzo-fused [4.3.1] carbon skeleton and the vicinal quaternary stereocenters. Other notable transformations include a tandem Michael/Mukaiyama aldol reaction to introduce most of the molecule's structural elements, along with hidden information for late-stage transformations, an intriguing tandem oxidative cyclization of a diene to form the bridged butyrolactone and enone moieties spontaneously, and a highly enantioselective hydrogenation of a cycloheptenone derivative (97% ee) that paved the way for the asymmetric synthesis of salimabromide.

In sharp contrast to terrestrial myxobacteria,[1] marine myxobacteria (*Enhygromyxa, Plesiocystis, Pseudoenhygromyxa, Haliangium*) have few known secondary metabolites.[2,3] Among the known natural products originating from marine myxobacteria, salimabromide, which was discovered by König and co-workers in 2013,[3] is the first to have been obtained from the *Plesiocystis/Enhygromyxa* clade of obligatory marine myxobacteria. Preliminary studies showed that it is a potent inhibitor of *Arthrobacter crystallopoietes*. Unfortunately, further evaluation of its biological activity was hampered by its extremely low natural abundance (only 0.5 mg was isolated from 64 L of culture), as well as the difficulty of cultivating marine myxobacteria compared with terrestrial myxobacteria.

Salimabromide has a unique benzo-fused [4.3.1] carbon skeleton bearing four contiguous stereocenters, including vicinal quaternary carboncenters. Interestingly, the aromatic ring is dibrominated; and the unusually bridged cycloheptenone moiety is fused to a butyrolactone ring. These structural features make salimabromide highly compact and conformationally rigid, as well as an appealing synthetic challenge. In 2015, Menche and Schmalzbauer reported the first stereoselective construction of its tricyclic core.[4a] In 2018, Magauer and co-workers successfully completed the first racemic total synthesis of salimabromide.[5] Soon after, Menche and co-workers achieved its first enantioselective synthesis and showcased the quite unusual almost racemic nature of natural salimabromide.[4b,6] Intriguingly, both research groups employed an in situ ketiminium-[2+2]-cycloaddition of a tetralin-tethered amide to build the central bridged carbon framework and a Baeyer−Villiger oxidation to form the butyrolactone part (Figure 1).[7] In contrast, we envisioned that an intramolecular radical cyclization of diene **3** mediated by hydrogen atom transfer (HAT) could be used to simultaneously build the key benzo-fused [4.3.1] carbon skeleton and the vicinal quaternary centers and that a subsequent novel tandem oxidative cyclization would complete a concise synthesis of salimabromide.

We commenced the synthesis by carrying out a tandem Michael/Mukaiyama aldol reaction[8] of cycloheptadienone **4** (Scheme 1). To our delight, the silyl enol ether intermediate generated by the initial conjugate addition of Grignard reagent **5a**[9] with **4**, reacted smoothly with **6a** in the presence of zinc bromide as a Lewis acid to give desired adduct **8** in 63% yield, accompanied by a 15% yield of hydrolyzed product **7**, which could easily be transformed to **8**. Next, an oxidative rearrangement of the tertiary allylic alcohol[10] resulting from addition of methyl lithium to cycloheptenone **8** was used to quickly access β-methyl substituted cycloheptenone **3a**, which was required for the planned HAT-mediated cyclization.

Since the pioneering studies by Baran and co-workers,[11] the HAT-promoted Giese reaction has been thoroughly investigated[12−14] and has found a wide array of synthetic applications because of its practicality.[15,16] Inspired by this prior work, we subjected diene **3b** to HAT conditions with various catalysts (Fe, Co, Mn, etc.)[15a] in combination with a number of reductants (silanes)[14a] and solvents (Table 1; for complete optimization efforts, see Supporting Information). However, the desired radical cyclization proved to be challenging: the undesired [1,5]-HAT process[17] always predominated, producing a large amount of undesired alkene **9b**. We attributed these results both to the difficulty of forming vicinal quaternary centers[18,19] because of steric hindrance during the cyclization and to the proximity of the initially generated tertiary radical to the hydrogen atom at the γ-position of the enone moiety, which was supported by DFT calculations (Figure 2). The best results were eventually obtained with iron catalysis. Despite the relatively low yield of desired adduct **10a** (28%), the reaction could easily be scaled up to produce gram quantities in a single operation.

Having obtained ample quantities of **10a**, which contains all the hidden information required for subsequent trans-

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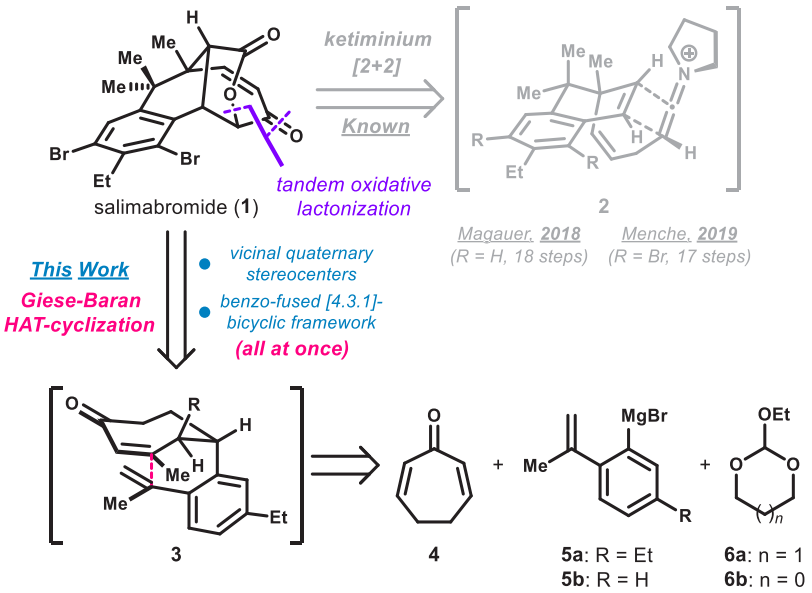
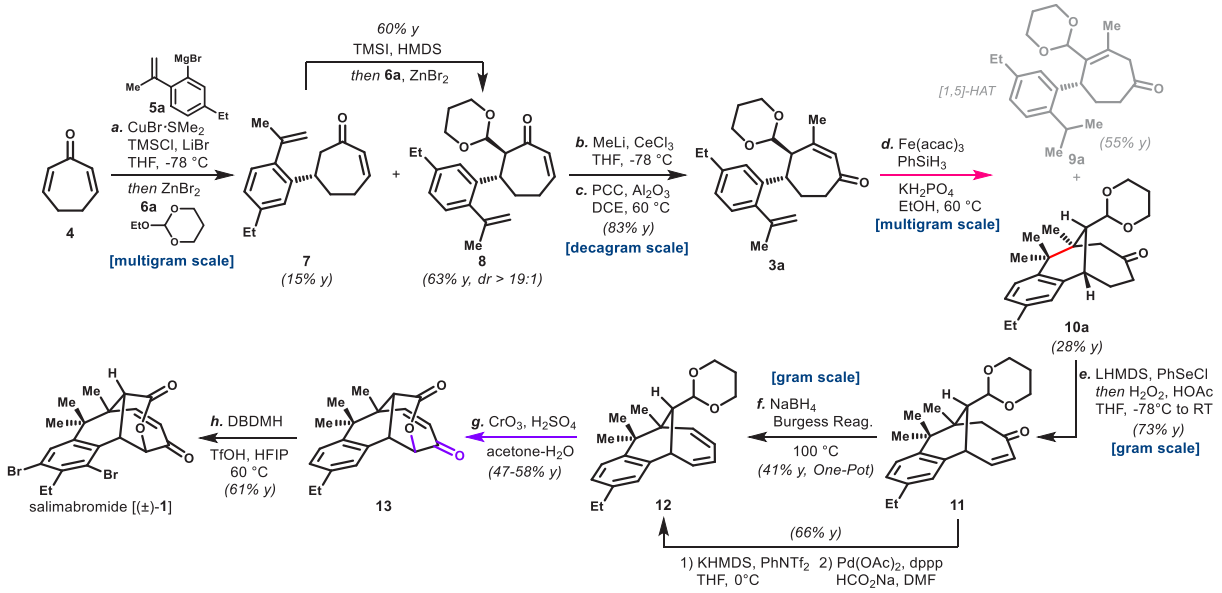


Figure 1. Previous work and our retrosynthetic analysis.

Scheme 1. Total Synthesis of Salimabromide [(±)-1].[a]



[a]See the Supporting Information for detailed procedures and characterization data.

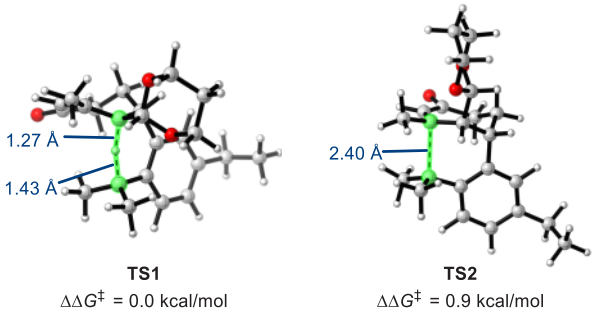


Figure 2. Comparison of optimized transition states leading to **9a** (**TS1**) and **10a** (**TS2**) from **3a** based on DFT calculations.

formations,[20,21] we moved forward to complete the synthesis of salimabromide. Dehydrogenation of **10a** quickly provided enone **11**, which was reduced and dehydrated to produce diene **12** initially. It is interesting to note that the dehydration was best performed with the Burgess reagent, and we found that this reduction-dehydration process could be carried out in one pot. To obtain a better overall yield, an alternative sequence (triflation-reduction) was later developed. At this stage, the lactone ring needs to be formed. To our delight, treatment of **12** with the Jones reagent directly and efficiently afforded butyrolactone ring-fused enone product **13**. Based on pioneering studies by McDonald and Towne who used hydroxy-directed alkene difunctionalizations for polyether synthesis,[22] we assumed that this tandem oxidative cyclization was directed by an acid intermediate generated in situ. This hypothesis was supported by preliminary experimental studies.[23] Finally, dibromination by utilizing the Brønsted acid-catalyzed halogenation of arenes recently disclosed by Jiao

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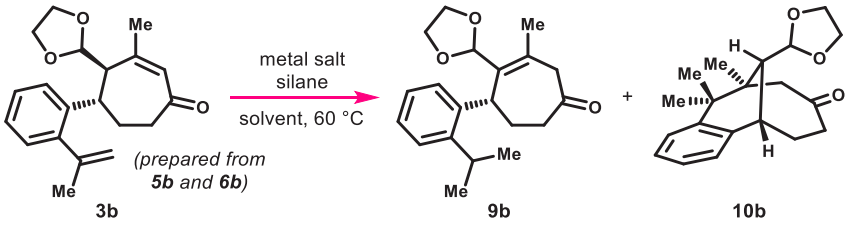
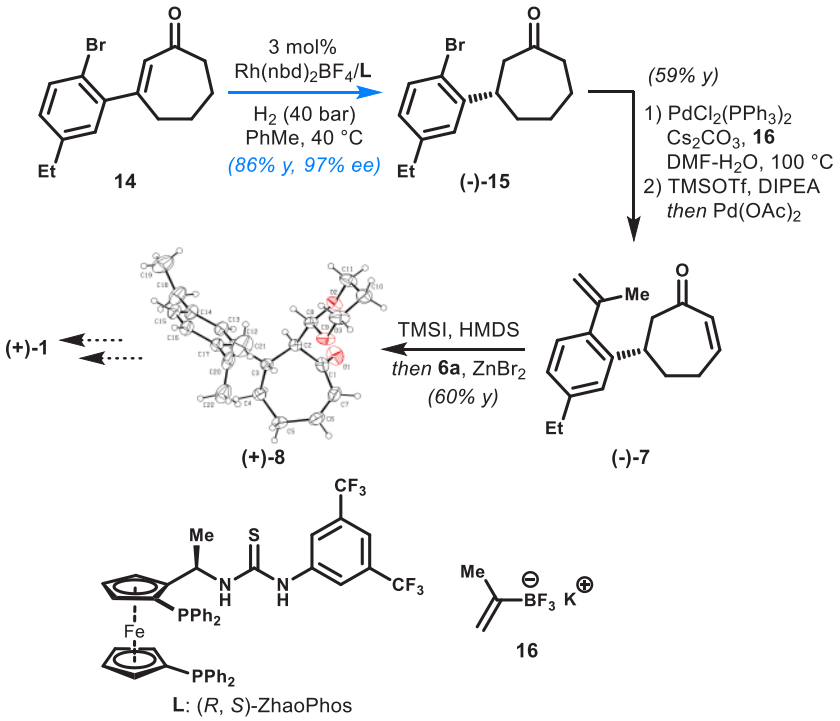
Table 1. Selected Optimization Data of the Giese–Baran Cyclization[a]



entry	metal salt	silane	solvent	yield (%)[b] 9b	10b
1[c]	$Mn(dpm)_3$	$PhSiH_3$	^{i}PrOH	4	17
2[c]	$Co(acac)_2$	$PhSiH_3$	^{i}PrOH	ND	ND
3	$Fe(acac)_3$	$PhSiH_3$	^{i}PrOH	11	22
4	$Fe(acac)_3$	$PhSiH_3$	EtOH	21	26
5	$Fe(acac)_3$	$PhSiH_3$	TFE	NR	NR
6	$Fe(acac)_3$	$PhSiH_3$	dioxane	33	15
7	$Fe(acac)_3$	$PhSiH_3$	DCE	NR	NR
8[d]	$Fe(acac)_3$	$PhSiH_2(O^{i}Pr)_2$	EtOH	4	21
9[d]	$Fe(acac)_3$	Et_3SiH	EtOH	NR	NR
10[d]	$Fe(acac)_3$	TMDSO	EtOH	NR	NR
11[d]	$Fe(acac)_3$	Ph_2SiH_2	EtOH	17	20
12[e]	$Fe(acac)_3$	$PhSiH_3$	EtOH	30	28

[a]Reaction conditi ons: **3b** (0.25 mmol), metal salt (0.3 equiv), and silane (3.0 equiv) in solvents under N_2 at 60 °C for 1–3 h. [b]Determined by crude NMR. [c]TBHP (2.0 equiv) was added. [d]Conducted at 40 °C. [e]KH_2PO_4 (2.0 equiv) was added. ND = Not Determined (messy). NR = No Reaction.

Scheme 2. Formal Enantioselective Total Synthesis of (+)-Salimabromide [(+)-1].[a]



[a]See the Supporting Information for detailed procedures and characterization data and X-ray data of (+)-**8** (CCDC 2205845; key: C, gray; H, white; O, red).

and co-workers was found to be superior to Magauer's protocol[5] and provided salimabromide in a better yield.[24]

We, then, sought to accomplish an enantioselective synthesis of salimabromide (Scheme 2). Initially, we attempted to realize an enantioselective version of the tandem Michael/Mukaiyama aldol reaction of cycloheptadienone **4** to produce chiral **8**. Unfortunately, the initial conjugate addition proved extremely challenging with an aryl Grignard reagent **5** or an aluminum or boronic acid reagent, and only racemic adducts were obtainable in our hands.[25−27] Inspired by a recent advance

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achieved by Zhang and co-workers on enantioselective hydrogenation of endocyclic enones,[28] we turned our attention to the enantioselective hydrogenation of cycloheptenone derivative **14**. To our delight, when we used (*R*,*S*)-ZhaoPhos as a ligand, reduction product (−)-**15** was obtained in 86% yield with 97% ee, for which the absolute configuration was determined by single-crystal X-ray analysis of its later intermediate (+)-**8**. Subsequent Suzuki coupling and dehydrogenation provided chiral enone (−)-**7**. Its transformation to (+)-**8** thus constitutes a formal asymmetric synthesis of (+)-salimabromide. Because (*S*,*R*)-ZhaoPhos is also easily accessible, we expect that the same sequence could be used to obtain (−)-salimabromide from the enantiomer of (−)-**15**.

In summary, we have achieved a concise synthesis of the marine natural product salimabromide by utilizing a novel intramolecular HAT-mediated radical cyclization to simultaneously construct the unique benzo-fused [4.3.1] carbon skeleton and the vicinal quaternary centers. In addition, the discovery and application of an unprecedented acid-directed tandem oxidative cyclization to form the bridged butyrolactone and enone moieties further enhanced the overall efficiency of the synthesis. Moreover, a highly enantioselective hydrogenation of a cycloheptenone intermediate (97% ee) paved the way for an enantioselective synthesis of (+)-salimabromide and would likely permit the synthesis of its enantiomer, (−)-salimabromide. We expect that the transformations described herein will have implications for future developments in the field of organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c08337.

Experimental procedures and characterization data for all the products (PDF)

Accession Codes

CCDC 2205845 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

PCC, pyridinium chlorochromate.; LHMDS, lithium bis(trimethylsilyl)amide.; Burgess reag., methyl *N*-(triethylammoniosulfonyl)carbamate; $Rh(nbd)_2BF_4$, bis(norbornadiene)rhodium(I) tetrafluoroborate.; DCE, 1,2-dichloroethane.; TFE, 2,2,2-trifluoroethanol.; HFIP, 1,1,1,3,3,3-hexafluoro-2-propanol.; DIPEA, *N*,*N*-diisopropylethylamine.; TMDSO, tetramethyldisiloxane.; DBDMH, 1,3-dibromo-5,5-dimethylhydantoin.; y, yield; dr, diastereomeric ratio; ee, enantiomeric excess

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