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# Total synthesis of (−)-funebrine via Au-catalyzed regio- and stereoselective γ-butyrolactonization of allenylsilane

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ABSTRACT

The stereoselective total synthesis of (−)-funebrine from 2-butyn-1-ol was described. The crucial steps in the synthesis involved the stereoselective enolate Claisen rearrangement of the (*S*)-α-acyloxy-α-alkynylsilane **8**, the Au-catalyzed regio- and stereoselective lactonization of the allenylsilane **7**, and the Paal–Knorr pyrrole condensation using an unsymmetrical 1,4-diketone **4b**.



The γ-butyrolactones are often found as a core substructure in many biologically active natural products. (−)-Funebrine (**1**),[1] isolated in 1984 from the flowers of *Quararibea funebris*, is a representative example of this class of natural products. This flower was used as a folk medicine for treating various diseases while the biological activity of **1** had not yet been elucidated. The structure is characterized by the highly functionalized γ-butyrolactone core with three contiguous stereogenic centers including an amino group on the lactone ring. Only two total syntheses of **1** including an enantioselective version have been reported.[2] Herein, we report the stereoselective total synthesis of (−)-**1** via the silyl group-directed Au-catalyzed regio- and stereoselective γ-butyrolactonization of the allenylsilane.

Ishibashi and co-workers reported the synthesis of **1** based on the coupling of the 2-amino γ-butyrolactone **3** with the symmetrical diketone **4a** (P = P′) to construct the pyrrole core **2**. We considered that the use of the unsymmetrical 1,4-diketone **4b** (P ≠ P′) would be advantageous in view of the efficient synthesis of an aldehyde **2** in comparison with the use of **4a**.[2] In a preceding paper, we described the Au-catalyzed conversion of the optically active (*S*,a*S*)-α-allenylsilane **7** to the (2*S*,3*S*)-2-amino-3-methyl-4-silylmethylene-γ-butyrolactone **6**, prepared from the enolate Claisen rearrangement of the (*S*)-α-acyloxy-α-alkynylsilane **8**.[3,4] Since the γ-butyrolactone **6** possessed both the requisite stereochemistry and functional groups on the lactone ring, this can be a plausible precursor for the synthesis of the key γ-butyrolactone **3** via the stereoselective reduction of **5** (Scheme 1).

Our preliminary studies indicated that the conversion of **6a** (*Si* = TBS) into **5** was accompanied by a troublesome epimerization at C3 to give a 1:1 mixture of diastereomers **5′** (Scheme 2). The undesired epimerization occurred during the removal of the TBS group from the α-silyl ketone **9** which was prepared by the hydrolysis of **6a** with $Na_2CO_3$.[5] To avoid the troublesome epimerization at C3, we chose **6b** possessing a dimethylphenylsilyl ($Me_2PhSi$) group, since this group is sterically less bulky than the TBS group and is readily removed under mild reaction conditions.

(*S*)-α-Acyloxysilane **8** (>95% ee) was prepared from the commercially available 2-butyn-1-ol by the following sequence of reactions (Scheme 3): (1) the reverse-Brook rearrangement of 2-butyn-1-ol (93%), (2) the Mukaiyama oxidation[6] of the resulting alcohol **10** (79%), (3) asymmetric reduction of the silyl ketone **11** using (+)-*B*-chlorodiisopinocamphenylborane (DIP-Cl),[7] and (4) condensation with Boc-Gly (2 steps, 87%). The enolate Claisen rearrangement of **8** gave the allenylsilane **7** (50%) with an excellent diastereoselectivity (>20:1).[4] The Au-catalyzed lactonization of **7** was performed using 3 mol % of $[(Ph_3PAu)_3]OBF_4$ to give the desired *trans* γ-butyrolactone **6b** in 69% yield. The catalyst loading could be reduced to 1 mol % by the addition of 20 mol % of *i*-$Pr_2NEt$. The fact that the observed dr had dropped to 10:1[8] as compared to that of the TBS group (>20:1) suggested that the decrease in the steric bulkiness of the silyl group significantly affected the diastereoselectivity of the γ-lactonization.[3] The treatment of the lactone **6b** with aqueous $Na_2CO_3$ simultaneously occurred with the lactone opening and the removal of the $Me_2PhSi$ group in a one-pot operation to give the methyl ester **5** as a single diastereomer after the $CH_2N_2$ treatment (71%, 2 steps).

Next, we examined the reduction of methyl ketone **5** to (4*R*)-amino lactone **3**. Initial attempts using the substrate-controlled

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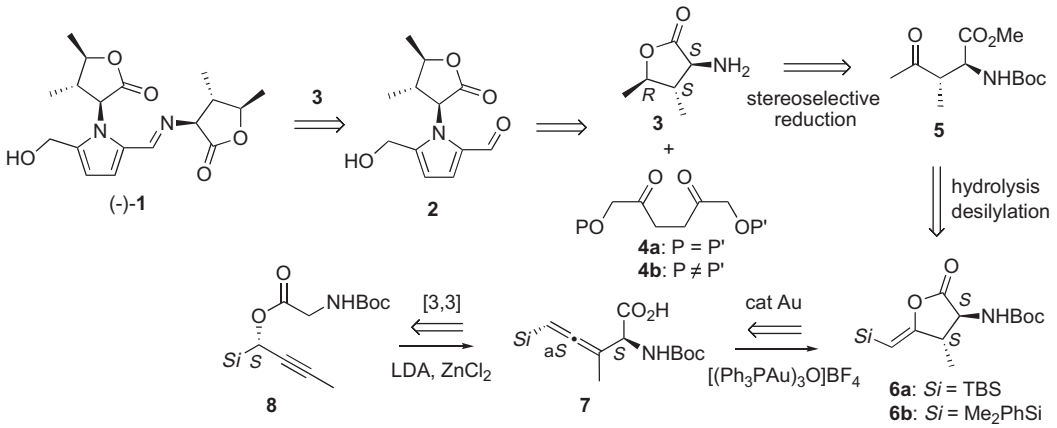
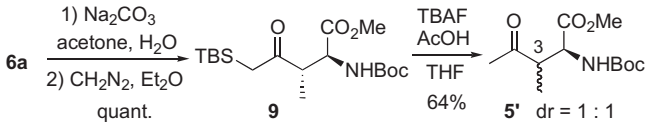



**Scheme 1.**

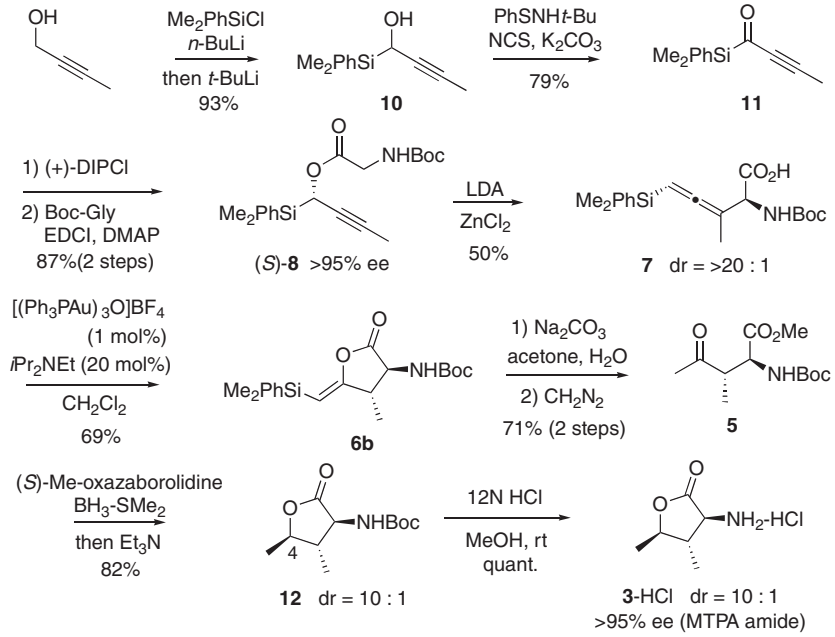



**Scheme 2.**

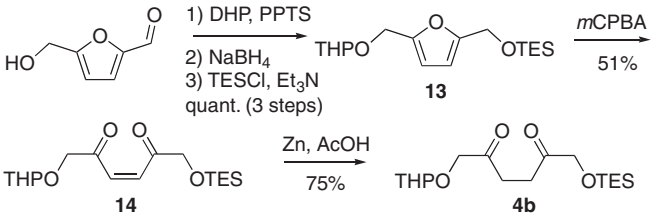
methods, that is, Felkin–Anh type or chelation-controlled reduction using hydride reagents, were not satisfactory enough to give a mixture of the desired (4*R*)- and undesired (4*S*)-lactones **12** (4*R*/4*S* = 3:1–1:20).[9] Therefore, we turned our attention to the use of a chiral oxazaborolidine for the reagent-controlled reduction. We found that (*S*)-Me-oxazaborolidine[10] solved this problem by producing (4*R*)-**12** as the major isomer (82%, dr = 10:1). The removal of the Boc group gave (2*S*,3*S*,4*R*)-**3**-HCl (quant., >95% ee, dr = 10:1). Since both undesired (4*S*)-isomers contaminated in **12** and **3** were inseparable under chromatographic as well as recrystallization conditions, respectively, further transformations were performed as the mixture (10:1).

The 1,4-diketone **4b** possessing the TES and THP protected hydroxymethyl groups, which can be selectively removed upon the exposure to fluoride ion or under acidic conditions, was synthesized from commercially available 5-hydroxymethyl furfural (Scheme 4). After the protection of the hydroxy group with the THP group, reduction of the aldehyde followed by the protection of the resulting alcohol with the TES group to give **13** (3 steps, quant). Oxidation of the furan with anhydrous *m*CPBA[11] furnished the enone **14** (51%), which, upon reduction with Zn/AcOH, afforded the unsymmetrical 1,4-diketone **4b** (75%).

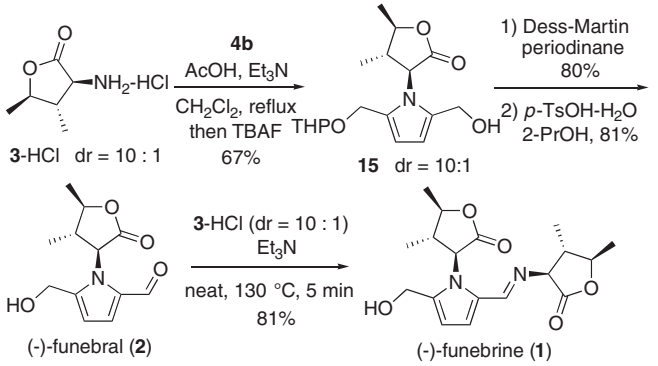
With the diketone **4b** in hand, we next examined the Paal–Knorr pyrrole condensation with the 2-amino-γ-lactone **3**, prepared in situ from **3**-HCl and $Et_3N$ (Scheme 5). The reaction was successfully performed by refluxing the mixture in $CH_2Cl_2$ in the presence of 5 equiv of AcOH.[11] The addition of TBAF to the reaction mixture effected the selective removal of the TES group to give the pyrrole **15** with a protection-free alcohol in 67% yield. The oxidation of **15** followed by the removal of the THP group gave (−)-funebral (**2**) (2 steps, 64%).[12] The minor isomer could be removed at this stage by column chromatography on silica gel. Finally, the imine




**Scheme 3.**



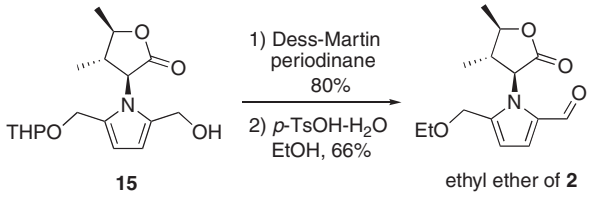

Scheme 4.




Scheme 5.

formation was accomplished by the condensation of **2** with **3** during heating at 130 °C[2a] to give (−)-**1** in 81% yield. All the spectral data including the optical rotation of synthetic **1** ($[\alpha]_D^{23}$ −69.2 (*c* 1.00, $CHCl_3$)) were in good agreement with those of the authentic data ($[\alpha]_D^{26}$ −71.3 (*c* 1.00, $CHCl_3$)).[2a]

In summary, the stereoselective synthesis of (−)-funebrine (**1**) was achieved from the commercially available 2-butyn-1-ol in 14 steps. The synthesis is highlighted by the construction of the two contiguous stereocenters at C2 and C3 by the enolate Claisen rearrangement of the (*S*)-α-acyloxy-α-alkynylsilane **8** and the Au-catalyzed lactonization of the resulting allenylsilane **7**. The pyrrole ring was constructed by the condensation of the unsymmetrical 1,4-diketone **4b** with the 2-amino-γ-lactone **3** under mild reaction conditions, which enabled the efficient conversion of the resulting pyrrole **15** to the natural funebrine (**1**). The biological evaluation of **1** is currently in progress in our laboratories.




Scheme 6.

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## Supplementary data

Supplementary data (full experimental details and characterization data of all synthetic compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.050.

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5. The methanolysis of **6a** using $K_2CO_3$ in MeOH gave **9** as a mixture of diastereomers (dr = 1:1).
6. Matsuo, J.; Iida, D.; Yamanaka, H.; Mukaiyama, T. *Tetrahedron* **2003**, *59*, 6739–6750.
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8. The 2,3-*trans*- and *cis* diastereomers **6b** (10:1) were separated by column chromatography on silica gel.
9. The (4*R*)-**12**/(4*S*)-**12** ratios using several reducing reagents were as follows: L-selectride (1:20), super hydride (1:2), $NaBH_4$ (3:1), and $Zn(BH_4)_2$ (1.5:1).
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12. Using EtOH instead of 2-PrOH as the solvent during the removal of the THP group, the ethyl ether of **2** was obtained in 66% yield (Scheme 6).