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Total Synthesis of (+)-Gracilamine Based on Oxidative Phenolic Coupling Reaction and Determination of its Absolute Configuration

Minami Odagi,* Yoshiharu Yamamoto, Kazuo Nagasawa*

Abstract: The first enantioselective total synthesis of (+)-gracilamine (**1**) was achieved, featuring a diastereoselective phenolic coupling reaction followed by a regioselective intramolecular aza-Michael reaction to construct the ABCE ring system. The stereochemistry at C3a in **1** is controlled by the stereocenter at C9a, which was selectively generated (91% ee) by utilizing an organocatalytic enantioselective aza-Friedel-Crafts reaction developed by our group. This synthesis reveals that the absolute configuration of (+)-gracilamine is (3a*R*, 4*S*, 5*S*, 6*R*, 7a*S*, 8*R*, 9a*S*).

(+)-Gracilamine (**1**) was isolated from *Galanthus gracilis* by Ünver and Kaya in 2005.[1] **1** contains a pentacyclic ring system with seven consecutive stereogenic centers, including an all-carbon quaternary stereocenter (Figure 1A). Because of this synthetically challenging structure, **1** has attracted considerable interest,[2,3] and total syntheses of **1** have been reported by groups led by Ma,[2a] Gao,[2b] and Banwell,[2e] while two other groups[2c,d] have reported formal total syntheses. However, no enantioselective synthesis of **1** has yet been reported, and the absolute configuration of (+)-**1** remains to be established. One of the key difficulties facing enantioselective synthesis of **1** is construction of the chiral stereocenter at C3a. In previous syntheses, the following strategies were applied for construction of this quaternary carbon center: (i) desymmetrized intramolecular 1,3-dipolar cycloaddition,[2a] (ii) photo-induced Nazarov reaction,[2b] (iii) intramolecular pyrone Diels-Alder reaction at high temperature,[2c] (iv) Pd(II)-catalyzed Alder-ene reaction,[2e] and (v) Rh(I)-catalyzed [3+2+1] cycloaddition[2d] (Figure 1A). Although these strategies are efficient and straightforward, synthesis of chiral precursors for these reactions proved very difficult, and only racemic products were obtained.

Oxidative phenolic coupling reaction using hypervalent iodine is a powerful method for constructing polycyclic ring systems,[4-6] and the resulting dienone is a useful building block for further transformations.[7] Indeed, oxidative phenolic coupling reactions have been widely applied for the synthesis of natural products.[8,9] However, the synthesis of fused rings via oxidative phenolic coupling is still challenging. In particular, synthesis of 5-membered rings has not been well explored, probably due to the highly strained nature of the resulting 6-5-6 membered ring system.[10,11] So far, only one successful example has been reported, with moderate yield (Figure 1B).[10] Nevertheless, in our synthesis of **1**, we aimed to apply oxidative phenolic coupling reaction to construct the 6-5-6 ring system in **1** with control of the stereocenter at C3a.

Enantioselective 1,2-type aza-Friedel-Crafts (aza-F-C) reaction of aldimines and phenols is efficient approach for the synthesis of optically active benzylamine derivatives. Therefore, numerous studies have been reported by using chiral metal- and organocatalysts in the past decades.[12,13] We have recently developed an enantioselective 1,2-type aza-F-C reaction of *N*-Boc aldimine with sesamol by using guanidine-bisthiourea bifunctional organocatalyst,[14] and we applied the reaction for the construction at C9a in **1**.

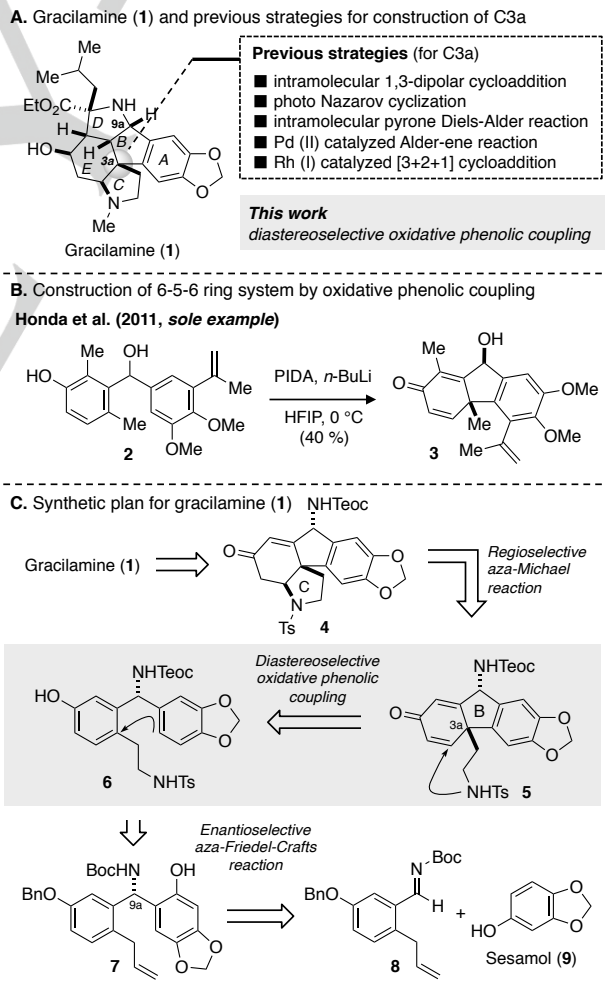

Figure 1. (A) Structure of gracilamine and illustration of previous strategies for constructing the C3a stereocenter; (B) sole reported example of the construction of a 6-5-6 ring system via oxidative phenolic coupling reaction; (C) our synthetic plan for gracilamine (**1**).

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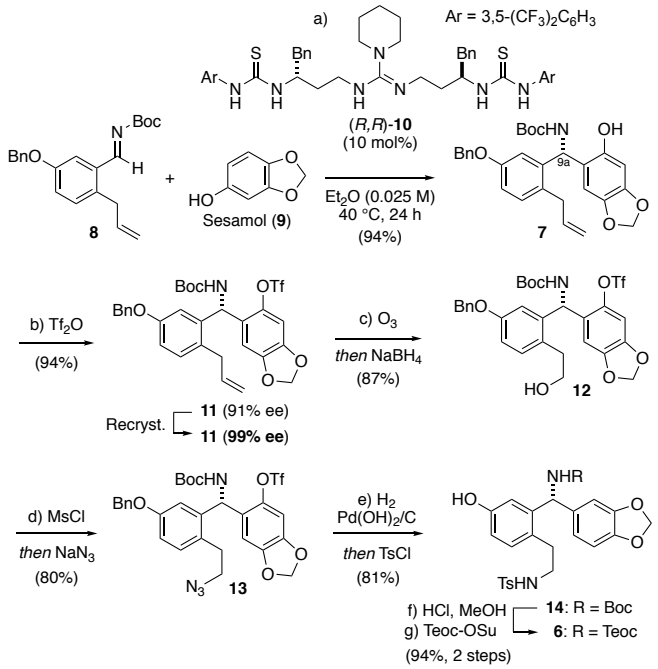
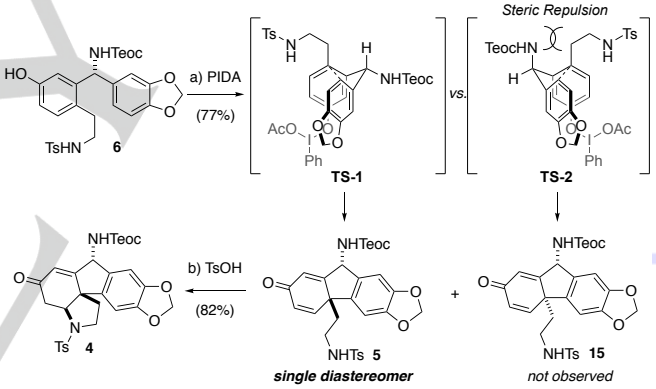


Scheme 1. Synthesis of phenolic coupling precursor **6**. Reagents and conditions: (a) (*R,R*)-**10** (10 mol%), Et_2O (0.025 M), 40 °C, 24 h, 94%; (b) Tf_2O (1.1 equiv), TEA (1.5 equiv), CH_2Cl_2, -78 °C, 30 min, 94%; (c) O_3, MeOH, -78 °C, 5 min, then $NaBH_4$ (10 equiv), -78 °C to rt, 1 h, 87%; (d) MsCl (3 equiv), TEA (5 equiv), DMF, 0 °C, 10 min, then NaN_3 (10 equiv), 60 °C, 6 h, 80%; (e) H_2, $Pd(OH)_2$/C (20 wt%), MeOH, 50 °C, 1 h, then TsCl, 0 °C to rt, 2 h, 81%; (f) 2 N HCl/MeOH, rt, 12 h; (g) Teoc-OSu (2 equiv), TEA (1.5 equiv), CH_2Cl_2, 0 °C, 2 h, 94% (2 steps). Boc = *tert*-butyloxycarbonyl, Bn = benzyl, TEA = triethylamine, Teoc-OSu = *N*-[2-(trimethylsilyl)ethoxycarbonyloxy]succinimide, Tf = trifluoromethanesulfonyl, Ts = *p*-toluenesulfonyl.

Our synthetic plan is depicted in Figure 1C. We envisioned that ketone **4**, a promising synthetic precursor for **1**,[2b] would be synthesized by successive construction of the B and C rings through diastereoselective oxidative phenolic coupling reaction of **6** followed by regioselective intramolecular aza-Michael reaction of dienone **5**. During synthesis of the B ring, stereoselective construction of the quaternary center at C3a was expected to be controlled by the stereochemistry at C9a in **6**, which could be constructed by organocatalytic aza-F-C reaction of sesamol (**9**) and *N*-Boc aldimine **8**.

Our synthesis of gracilamine (**1**) commenced with construction of the stereocenter at C9a by means of our organocatalytic enantioselective aza-F-C reaction of aldimines and phenols.[14] The reaction with *N*-Boc aldimine **8**, which was synthesized from 3-hydroxybenzoic acid in seven steps,[15] and sesamol (**9**) was examined in the presence of guanidine-bisthiourea bifunctional organocatalyst (*R,R*)-**10**. Under the previously developed conditions, aza-Friedel-Crafts reaction took place smoothly, and the corresponding *N*-Boc amine **7** was obtained in 94% yield. The enantioselectivity of **7** was determined to be 91% ee by chiral HPLC after conversion to the triflate **11**.[16] The ee value of **11** was increased to 99% after a single recrystallization from hexane. Then, ozonolysis of the double bond in **11** followed by treatment with $NaBH_4$ gave primary alcohol **12** in 87% yield. The azide group was introduced into **12** by treatment with MsCl followed by reaction with NaN_3 in DMF to give **13** in 80% yield. Then, reduction of the azide group and triflyloxy group, and deprotection of the benzyl group in **13** were carried out simultaneously under hydrogenolysis conditions, and the resulting amine was protected with a tosyl group to give phenol **14** in 81% yield in two steps. The Boc group in **14** was then converted into a Teoc group by reaction with hydrochloric acid followed by Teoc-OSu, affording **6** in 94% yield (Scheme 1).[17]

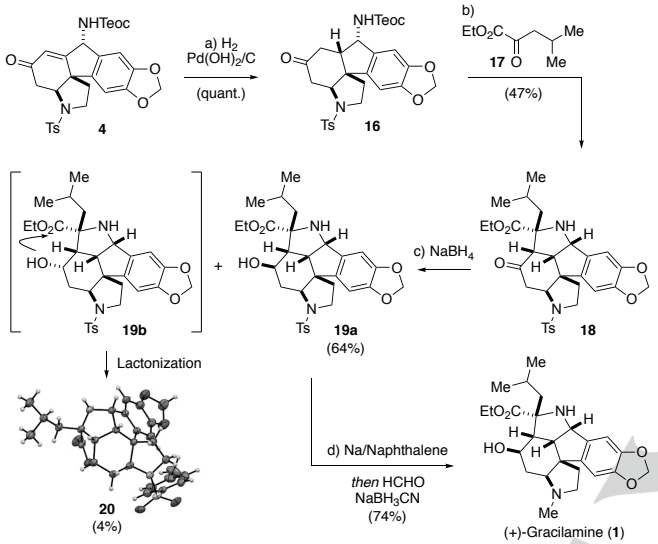
With phenol **6** in hand, we examined the oxidative phenolic coupling reaction for constructing the 6-5-6 ring system corresponding to the A-B-E rings of **1**. Thus, phenol **6** was subjected to PIDA in hexafluoro-2-propanol (HFIP) at high dilution (0.01 M) at 0 °C.[18] Under these conditions, coupling reaction took place to afford dienone **5** in 77% yield as a single diastereomer. In this reaction, two possible transition states of **TS-1** and **TS-2** regarding the stereochemistry at C9 can be considered, but the sterically less hindered **TS-1** should be preferred, and indeed, the desired **5** with *S* configuration at C3a was obtained predominantly (Scheme 2). Then, regioselective intramolecular aza-Michael reaction of **5** was investigated. After several attempts, the enone **4** was selectively obtained in 82% yield by treatment with *para*-toluenesulfonic acid.



Scheme 2. Oxidative phenolic coupling reaction followed by aza-Michael reaction of **6**. Reagents and conditions: (a) PIDA (1.0 equiv), HFIP (0.01 M), 0 °C, 30 min, 77%; (b) $TsOH \cdot H_2O$ (10.0 equiv), CH_2Cl_2, 0 °C, 10 min, 82%. HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol, PIDA = iodobenzene diacetate.

Thus, total synthesis of (+)-gracilamine (**1**) from **4** was accomplished in five steps (Scheme 3). The olefin moiety of **4** was hydrogenated in the presence of palladium hydroxide on carbon under a hydrogen atmosphere to give ketone **16** quantitatively. Then, we examined construction of the D-ring of **16** with α-keto ester **17** by intramolecular 5-*endo*-trig Mannich-type reaction. First, we followed Gao's protocol,[2b] i.e., we used 3 equiv. of **17** in $CHCl_3$/TFA = 1:1 at 66 °C, but only a trace amount of **18** was obtained. We further examined the reaction conditions, and found that cyclopentyl methyl ether (CPME) was effective as a solvent for this reaction, and **18** was obtained in 47% yield. Reduction of the ketone in **18** was conducted with sodium borohydride to give the alcohol **19a** (64%) and its diastereomer **19b** (dr. = 16:1), which was simultaneously cyclized to lactone **20** in 4% yield. The structure of **20** was

confirmed by X-ray crystallography.[19] Finally, (+)-gracilamine (**1**) was obtained from **19a** by removal of the tosyl group with sodium and naphthalene, followed by reductive methylation of the amine with formaldehyde in the presence of sodium cyanoborohydride in 74% yield. The ^{1}H and ^{13}C NMR spectral data of synthetic **1** were identical with those of natural (+)-**1** as reported in the literature. In addition, the optical rotation of synthetic **1** [$[\alpha]_D^{25}$ = +16.4 (*c* 0.11, MeOH)] was consistent with that of natural **1** [$[\alpha]_D^{25}$ = +21.8 (*c* 0.13, MeOH)].[1] Thus, this synthesis revealed that the absolute configuration of natural (+)-gracilamine (**1**) is (3a*R*, 4*S*, 5*S*, 6*R*, 7a*S*, 8*R*, 9a*S*).



Scheme 3. Total synthesis of gracilamine (**1**). Reagents and conditions: (a) H_2, $Pd(OH)_2$/C (30 wt%), THF, rt, 30 min, quant.; (b) **3** (10.0 equiv.), CPME/TFA = 1:1, 70 °C, 2 h, 47%; (c) $NaBH_4$ (10.0 equiv.), THF/MeOH = 1:1, 0 °C to rt, 30 min, **19**: 64%, **20**: 4%; (d) Na/naphthalene (3.0 equiv), THF, -78 °C, 10 min, then 37% HCHO aq. (1.0 equiv), $NaBH_3CN$ (1.0 equiv), 0 °C, 30 min, 74%. CPME = cyclopentyl methyl ether, TFA = trifluoroacetic acid, THF = tetrahydrofuran.

In summary, we have accomplished the first enantioselective total synthesis of (+)-gracilamine (**1**) in 23 steps with 1% overall yield from the commercially available 3-hydroxybenzoic acid. Our synthetic strategy features (i) enantioselective aza-Friedel-Crafts reaction of imine **8** and sesamol (**9**) by using guanidine-bisthiourea bifunctional organocatalyst (*R,R*)-**10** to construct the stereocenter at C9a, which controls all the other stereocenters in **1**, and (ii) diastereoselective oxidative phenolic coupling reaction of **6** to afford **5** for construction of the quaternary stereocenter at C3a, followed by regioselective intramolecular aza-Michael reaction. The absolute configuration of (+)-**1** was determined by this synthesis.

Acknowledgements

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Keywords: natural product • total synthesis • oxidative phenolic coupling reaction • organocatalyst • aza-Friedel-Crafts reaction

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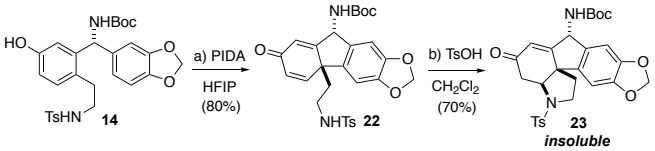
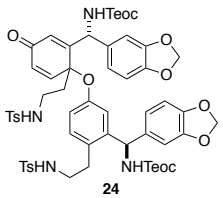
[15] For details of the synthesis of imine **8**, see Supporting Information.

[16] For HPLC charts, see Supporting information.

[17] An oxidative phenolic coupling of **14** and following the aza-Michael reaction took place smoothly to give enone **23** in high yield. However, further transformation was difficult due to the solubility problem of **23** in various organic solvents.



[18] At the concentration of 0.1 M, dimeric product **24** was generated as a side-product.



[19] See Supporting Information for the X-ray structure. The crystallographic data (CCDC1558467) can be obtained free of charge from The Cambridge Crystallographic Data Center.

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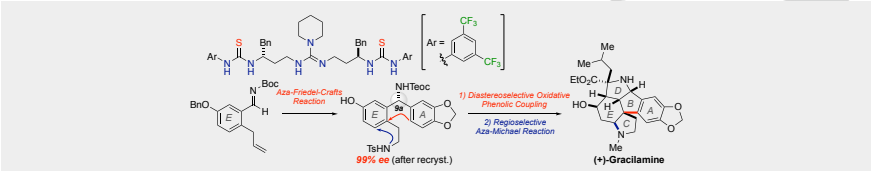

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