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Synthetic Methods

Total Synthesis of (−)-Isoschizogamine

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Abstract: The total synthesis of (−)-isoschizogamine was accomplished, featuring the construction of the quaternary carbon center by the modified Johnson–Claisen rearrangement in basic media and the facile assembly of the key tetracyclic quinolone intermediate through a cascade cyclization. The characteristic cyclic aminal was constructed by late-stage C–H functionalization at the position adjacent to the lactam nitrogen using a combination of CrO_3 and nBu_4NIO_4 and subsequent $Bi(OTf)_3$-mediated cyclization.

Isoschizogamine (**1**), isoschizogaline (**2**), and their congeners (**3**-**6**) were isolated from *Schizozygia caffaeoides* (Boj.) Baill, which grows in the tropical zone of East Africa (Figure 1).[1] The plant extract exhibits antimicrobial activity and has been used in Kenya as a transitional medicine.[2] The structure of **1** was initially considered as an epimer of schizogamine (**5**) at the C-7 position.[1] In 1998, however, Hájicek and co-workers proposed a revised structure for **1**, which possesses a densely fused hexacyclic skeleton including a tetrasubstituted aminal carbon and quaternary carbon center.[3] Although the structures of **1** and **2** inspired a great number of synthetic studies,[4] only one racemic[5] and two enantioselective[6] total syntheses of **1** have been reported to date. Herein, we describe the asymmetric total synthesis of isoschizogamine (**1**) through late-stage C–H functionalization and a cyclic aminal formation.

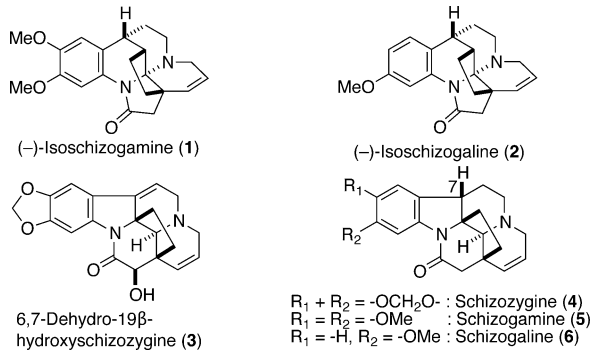
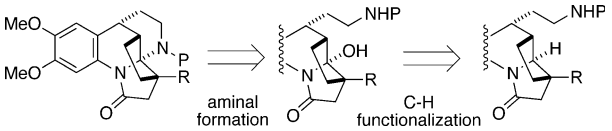


Figure 1. Schizozygane alkaloids.

The construction of the densely fused polycyclic skeleton bearing oxygen and/or nitrogen functionalities represents a formidable challenge to the current state of the art in organic synthesis.[7] One of the directions to solving this problem would be a rapid framework assembly, taking advantage of the simultaneous multiple bond formation through one-pot cascade reactions, and late-stage functionalization of the framework.[8] The most challenging task in synthesizing **1** is considered to be the construction of the aminal at the hindered position adjacent to the quaternary carbon center. In the present study, we attempted to construct the aminal structure from the corresponding lactam derivative by oxidizing the C(sp^3)–H bond adjacent to the lactam amine and subsequently forming the cyclic aminal (Scheme 1). This late-stage C–H functionalization strategy[9] should enable the rapid assembly of the fully elaborated aminal compound precursor by lowering the oxidation state of each intermediate.



Scheme 1. C–H oxidation and cyclic aminal formation strategy.

Scheme 2 presents an outline of the conducted retrosynthetic analysis. The hexacyclic skeleton of **1** would be formed by ring-closing olefin metathesis of diene **7**.[10] As discussed above, the cyclic aminal formation would be realized by establishing chemoselective oxidation of **9** at the C(sp^3)–H bond adjacent to the lactam amine and subsequent cyclization. As a result, the tetracyclic skeleton could be constructed rapidly from ketoaldehyde **11** with an aniline appendage through a triple cyclization cascade[11] initiated by intramolecular aldol condensation and aza-Michael addition. We expected that steric bias of the asymmetric quaternary carbon center would determine the stereochemical outcome of cascade cyclization. The optically active **11** would be readily prepared by the chemoselective addition of aryl Grignard reagent to aldehyde **12**, which should be accessed from allylic alcohol **14** by the Johnson–Claisen rearrangement and oxidative cleavage of the double bond.

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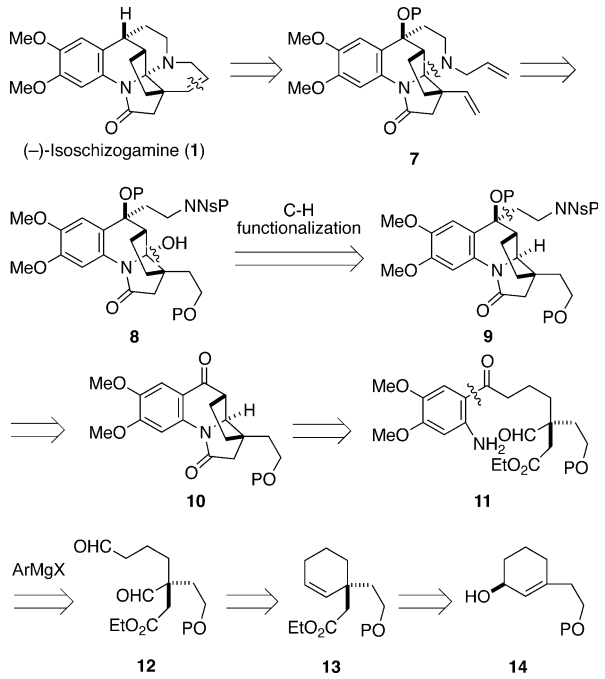
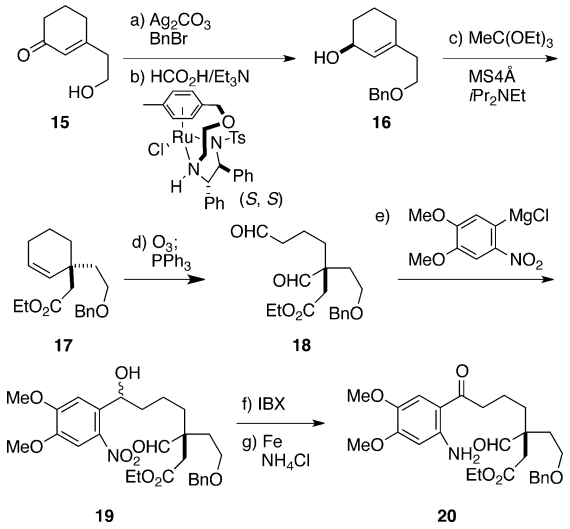


Scheme 2. Retrosynthetic analysis.

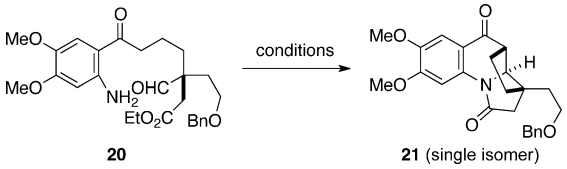


Scheme 3. Preparation of the substrate **20** for the cascade cyclization through the modified Johnson–Claisen rearrangement. Reagents and conditions: a) Ag_2CO_3, BnBr, CH_2Cl_2, RT, 90% yield; b) Ru* catalyst (0.5 mol%), HCO_2H/Et_3N, RT, 89% yield, 95% *ee*; c) $MeC(OEt)_3$, MS 4 Å, iPr_2NEt, 180 °C, MWI, 55% yield; d) O_3, CH_2Cl_2, −78 °C; PPh_3, −78 °C to RT, 66% yield; e) 4,5-dimethoxy-2-nitrobenzenemagnesium chloride, THF, −40 to −20 °C, 46% yield; f) IBX, MeCN, reflux, 86% yield; g) Fe, NH_4Cl, $EtOH/H_2O$, 80 °C, 90% yield; MS = molecular sieves, MWI = microwave irradiation, THF = tetrahydrofuran, IBX = *o*-iodoxybenzoic acid.

Our total synthesis commenced with the enantioselective construction of the quaternary carbon center by the Johnson–Claisen rearrangement (Scheme 3). The protection of the alcohol **15**[12] as benzyl ether and subsequent asymmetric 1,2-reduction following Ikariya's protocol[13] produces allyl alcohol **16** in a high yield and enantiomeric excess. However, the conventional Johnson–Claisen rearrangement[14] in the presence of weak acids resulted in formation of a complex mixture. After extensive investigation,[15] we determined that the Johnson–Claisen rearrangement could proceed in the presence of MS 4 Å although the optical purity was decreased. Further investigation on solvent effects revealed that reaction in a basic media suppressed the loss of optical purity. Thus, heating a Hünig's base solution of the reaction mixture in the presence of MS 4 Å under microwave irradiation promoted the Johnson–Claisen rearrangement to produce the desired ester **17** in 55% yield without the loss of optical purity. The cyclohexene ring was then cleaved by ozonolysis to provide the dialdehyde **18**, which reacted at the less sterically hindered aldehyde with the aryl Grignard reagent[16] to afford the benzyl alcohol **19**. Finally, the oxidation of benzylic alcohol to aryl ketone and reduction of the nitro group provided the substrate **20** for cascade cyclization.

The initial cascade cyclization trial (Table 1) under basic conditions produced a complex mixture comprising intramolecular aldol cyclization product **22** and other unidentified byproducts (Table 1, entry 1). Camphorsulfonic acid effectively resulted in

Table 1. Optimization of the triple cyclization cascade.

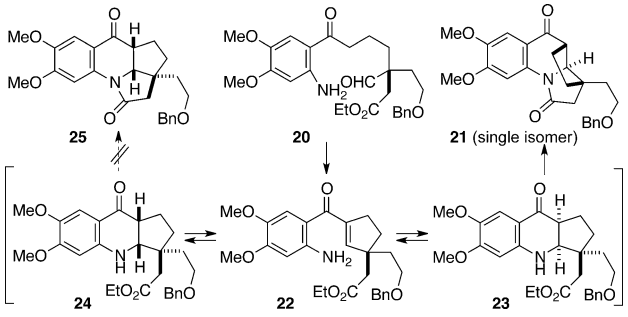


Entry	Reagent	Solvent	Temp. [°C]	Time [h]	Yield[a] [%]
1	K_2CO_3	MeOH	80	24	–
2	CSA	CPME	80	13	36
3	CSA	DMSO[b]	80	12	51

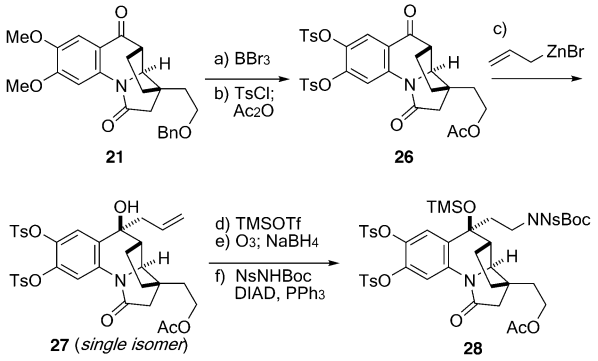
[a] Isolated yield. [b] Degassed solvent was used: CSA = camphorsufonic acid, CPME = cyclopentyl methyl ether, DMSO = dimethyl sulfoxide.

sequential triple cyclizations including the intramolecular aldol condensation, aza-Michael addition, and acid-mediated lactamization in one-pot to provide the desired tetracyclic compound **21** as a single isomer, although the yield was low (entry 2). The yield was improved by conducting the reaction at 150 °C in DMSO, producing **21** in 51% yield (entry 3). The excellent observed stereoselectivity should imply equilibrium between the two quinolone derivatives **23** and **24** via **22**, and only **23** underwent lactamization to generate the less strained *cis*-fused lactam **21** (Scheme 4).

Before examining the C–H functionalization, we processed the tetracyclic quinolone **21** to derive **28** to install the requisite side chain for the formation of the cyclic aminal (Scheme 5). First, two methyl ethers and benzyl ether were cleaved[17] and the resultant alcohol was treated with TsCl and acetic anhydride to produce **26**. To reduce electron density of the benzene ring and achieve chemoselective oxidation (see below), it was essential to convert the methoxy groups to tosyloxy groups. 1,2-Addition of allyl zinc reagent proceeded smoothly



Scheme 4. Plausible reaction mechanisms for the diastereoselective triple cyclization cascade.

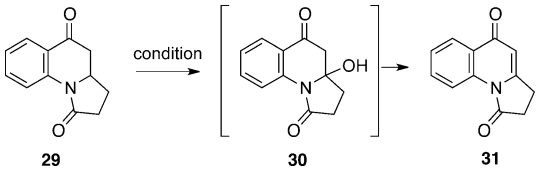


Scheme 5. Introduction of amino side chain. Reagents and conditions: a) BBr_3, pentamethylbenzene, CH_2Cl_2, −20 °C; b) TsCl, Et_3N, CH_2Cl_2, −20 °C; Ac_2O, DMAP, RT, 70% yield (two steps); c) allylzinc bromide, THF, 0 °C, 93% yield; d) TMSOTf, 2,6-lutidine, CH_2Cl_2, −20 °C, 95% yield; e) O_3, CH_2Cl_2/MeOH, −78 °C; $NaBH_4$, RT, 67% yield; f) NsNHBoc, DIAD, PPh_3, THF/toluene, RT to 60 °C, 96% yield; Ts = *p*-toluenesulfonyl, DMAP = 4-(dimethylamino)pyridine, TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl, Ns = 2-nitrobenzenesulfonyl, Boc = *t*-butoxycarbonyl, DIAD = diisopropyl azodicarboxylate.

to give the homoallyl alcohol **27** as a sole isomer, which was converted to the protected primary amine **28** through a sequence, including alcohol silylation, ozonolysis, and reductive treatments with $NaBH_4$ to afford the corresponding primary alcohol, and the Mitsunobu reaction to install the doubly-protected amino group.

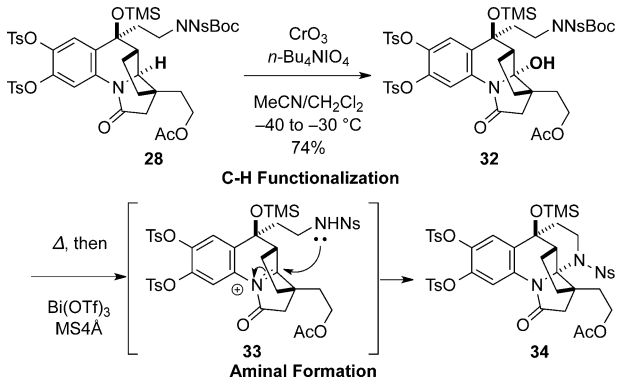
Thereafter, we investigated the key C–H oxidation. Initially, we examined various oxidants using a simple model compound **29** to explore the possible oxidation conditions (Table 2). The oxidation conditions with Ru,[18] which were previously reported as effective for the oxidation of amines, resulted in a complex mixture (Table 2, entry 1). In contrast, a combination of $Cr(CO)_6$ and *t*BuOOH[19] did give the expected elimination product **31** via hemiaminal **30** in low yield (entry 2). Screening several other conditions, we eventually found that the Fuchs' conditions using a combination of CrO_3 and nBu_4NIO_4[20] were effective. As a result, we succeeded in the chemoselective C–H oxidation at the position adjacent to the nitrogen atom and obtained the corresponding elimination product **31** (entry 3). Furthermore, the Fuchs' conditions also successfully facilitated the oxidation of **28** to furnish the hemiaminal **32** in high yield (Scheme 6). Finally, the cyclic aminal

Table 2. Investigation of C–H functionalization with model compound.



Entry	Reagents	Solvents	Temp. [°C]	Time [h]	Yield[a] [%]
1	$RuCl_2(PPh_3)_3$ *t*BuOOH	toluene	80	22	–
2	$Cr(CO)_6$ *t*BuOOH	MeCN	reflux	28	18
3	CrO_3 nBu_4NIO_4	$MeCN/CH_2Cl_2$	−20 °C	1	53

[a] Isolated yield.

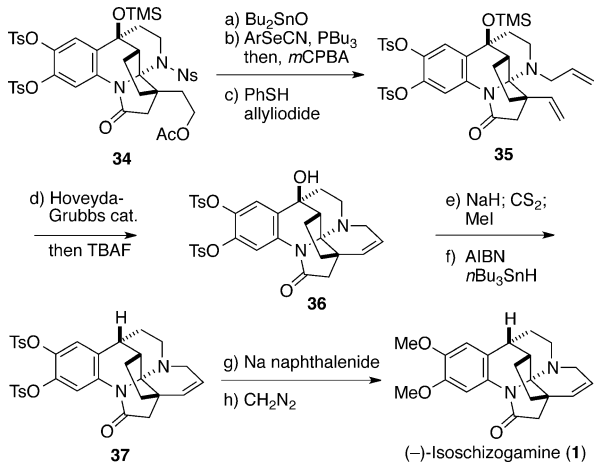


Scheme 6. C–H oxidation and aminal formation. Reagents and conditions: neat, 175 °C; $Bi(OTf)_3$, MS 4 Å, CH_2Cl_2, RT, 77% yield.

was constructed by thermally removing the Boc group and subsequently treating with $Bi(OTf)_3$ in the presence of MS 4 Å.[21]

The endgame of the total synthesis of (−)-isoschizogamine (**1**) is depicted in Scheme 7. First, the acetate **34** was converted to the diene **35** by removing the acetyl group with Bu_2SnO,[22] dehydrating the resultant primary alcohol using the Grieco–Nishizawa protocol,[23] and installing the *N*-allyl group under *N*-allylation conditions after the removal of the nosyl group.[24] The dehydropiperidine ring was formed by ring-closing metathesis using the Hoveyda–Grubbs second-generation catalyst[10] in the presence of benzoquinone and following desilyation was conducted with TBAF.[25] We effectively removed the hydroxy group by desilyation and subsequent Barton–McCombie deoxygenation protocol[26] to provide **37**. Finally, the two tosyl groups were reductively cleaved and subsequently methylated using diazomethane furnished (−)-isoschizogamine (**1**), which was in agreement with all the previously reported data.[3]

In conclusion, we accomplished the asymmetric total synthesis of (−)-isoschizogamine. The most significant synthesis steps include the facile construction of the tetracyclic quinolone intermediate by diastereoselective triple cyclization cascade and construction of the cyclic aminal structure through the late-stage C–H functionalization.



Scheme 7. Total synthesis of (−)-isoschizogamine. a) Bu_2SnO, toluene, reflux, 90% yield; b) 2-nitrobenzeneselenyl cyanide, PBu_3, CH_2Cl_2, 0 °C to RT; *m*CPBA, RT, 73% yield; c) PhSH, Cs_2CO_3, MeCN, 50 °C; allyl iodide, 40 °C, 63% yield; d) the second-generation Hoveyda–Grubbs catalyst (10 mol%), 1,4-benzoquinone, CH_2Cl_2, RT to 40 °C; TBAF, RT, 71% yield; e) NaH, THF, 0 °C; CS_2, RT; MeI, 64% yield; f) AIBN, nBu_3SnH, toluene, 80 °C, 87% yield; g) Na naphthalenide, THF, 0 °C; h) CH_2N_2, Et_2O/CH_2Cl_2/MeOH, 0 °C to RT, 94% yield (two steps); *m*CPBA = *m*-chloroperbenzoic acid, TBAF = tetra-*n*-butylammonium fluoride, AIBN = 2,2′-azo bisisobutyronitrile.

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Keywords: alkaloids · aminal · cascade reaction · C–H functionalization · total synthesis

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