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Total Synthesis of (−)-Isoschizogamine

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Supporting Information

ABSTRACT: A first asymmetric total synthesis of (−)-isoschizogamine has been accomplished. Our synthesis features the facile construction of the carbon framework of the natural product through a Wagner−Meerwein rearrangement, a tandem metathesis, a stereoselective rhodium-mediated 1,4-addition of an arylboronic acid, and a ring-closing metathesis via a hemiaminal ether.

Isoschizogamine (**1**, Figure 1) was isolated in 1963 from *Schizozygia caffaeoides*,[1] whose structure was initially assigned as an epimer at the C-7 position of the related indole alkaloid, schizogamine (**2**).[2] Intensive NMR studies led to the revision of the structure of **1** as a highly fused hexacyclic compound containing tetrahydroquinoline, hexahydroquinolizine, and pyrrolidinone moieties.[3] The two nitrogen atoms of these heterocycles form an aminal that is adjacent to a quaternary carbon. These fascinating structural features have attracted the attention of synthetic chemists, and one racemic total synthesis by Heathcock[4] and two synthetic studies[5] have been reported to date. Herein we disclose a novel total synthesis of isoschizogamine that features a unique approach to the construction of the carbon framework.

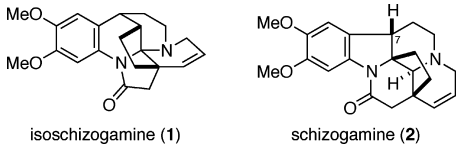
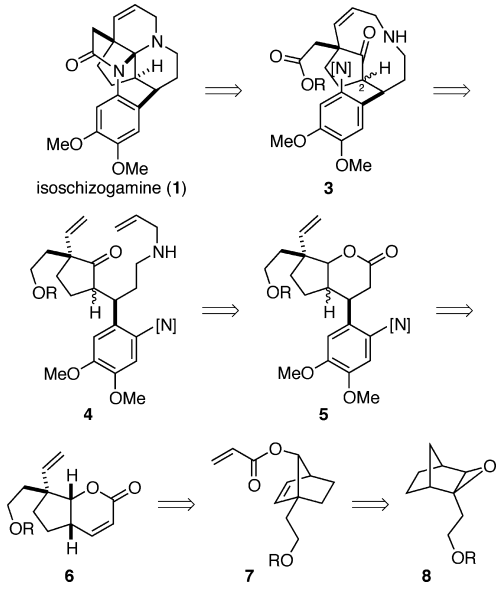


Figure 1. Isoschizogamine and schizogamine.

As shown in our retrosynthesis (Scheme 1), the aminal moiety would be constructed from diaminoketone **3**. The stereochemistry at C-2 could be controlled by enolization of the ketone at a later stage of the synthesis.[4] The double bond in **3** would be constructed by a ring-closing metathesis of diene **4**. An aromatic moiety of **4** could be incorporated via a 1,4-addition to the α,β-unsaturated lactone **6**. The *cis*-fused bicyclic lactone **6** is expected to control the stereoselectivity of the 1,4-addition. The bicyclic lactone **6** could be prepared by a tandem metathesis of bicyclo[2.2.1]heptene **7**, which would in turn be derived from norbornene oxide **8** via a Wagner−Meerwein rearrangement.[6]

Our synthesis commenced with the preparation of norbornene oxide **12** by means of the Shapiro reaction (Scheme 2). Oxidation of (+)-*exo*-norborneol[7] **9** by treatment with TPAP and NMO[8] afforded a ketone, which was converted into the corresponding trisyl hydrazone **10**. Upon treatment with *s*-butyllithium, **10** underwent the Shapiro reaction[9] to give an alkenyllithium species, which was treated sequentially with ethylene oxide and TBDPSCl to afford **11** in 79% yield. Epoxidation of **11** with *m*CPBA proceeded stereoselectively to furnish norbornene oxide **12**.

Scheme 1. Retrosynthesis



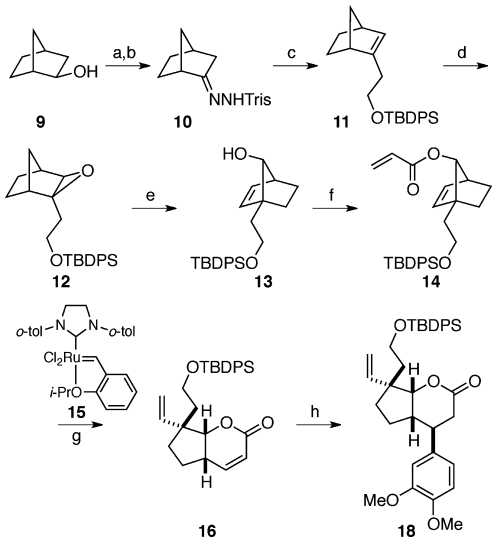
With the requisite norbornene oxide in hand, we next attempted the key Wagner−Meerwein rearrangement. According to Kleinfelter's procedure,[6] **12** was treated with phenylmagnesium bromide in refluxing ether. While the reaction of 2-phenylnorbornene oxide with phenylmagnesium bromide was reported to form the *gem*-diphenyl product,[6] **12** underwent the desired rearrangement to give **13** in 40% yield. The yield was further optimized by careful selection of the substituent on the aryl group and the halide ion in the Grignard reagent. The optimal conditions were achieved when **12** was treated with *o*-tolylmagnesium iodide in refluxing ether, giving **13** in 68% yield. The hydroxy group in **13** was acylated with acryloyl chloride to give **14** in 96% yield.

The crucial tandem metathesis to construct bicyclic lactone **16** required an extensive investigation of the reaction conditions. The literature precedents suggested that the *syn*-substitution to the double bond at the C7 position of the norbornene would lower the reactivity of the double bond in metathesis reactions.[10] Indeed, treatment of **14** with the

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Scheme 2[a]



[a]Reagents and conditions: (a) TPAP, NMO, MS4A, CH_2Cl_2, rt; (b) $TrisNHNH_2$, conc HCl, MeCN, rt, 96% (2 steps); (c) *s*-BuLi, THF, −78 to 0 °C; ethylene oxide in THF (1.2 M), −78 to 0 °C; TBDPSCl, rt, 79%; (d) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 93%; (e) *o*-tolMgI, Et_2O, reflux, 68%; (f) acryloyl chloride, *i*-Pr_2NEt, CH_2Cl_2, 96%; (g) Ru catalyst **15**, 1,6-heptadiene, benzene, 60 °C, 73%; (h) 3,4-$(MeO)_2C_6H_3B(OH)_2$ (**17**), $[RhCl(cod)]_2$, Et_3N, aq dioxane, rt, 93%.

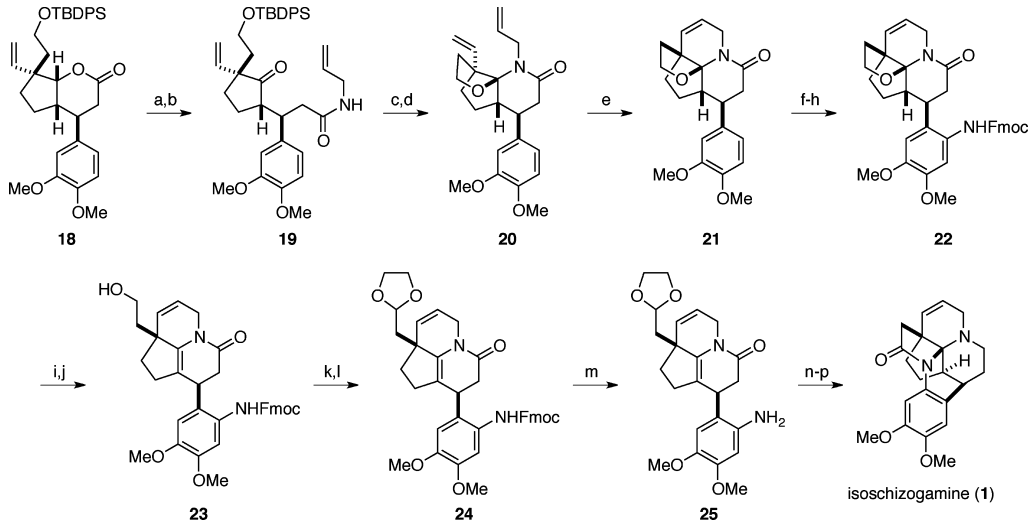
second-generation Hoveyda−Grubbs catalyst[11] in refluxing benzene afforded **16** in only 24% yield. Gratifyingly, we found that the use of the highly reactive catalyst **15**[12] in the presence of 1,6-heptadiene improved the yield of **16** to 73% yield. A subsequent rhodium-catalyzed 1,4-addition of arylboronic acid **17** to **16** proceeded smoothly with complete stereoselectivity to furnish **18**.[13]

Having established an efficient route to the key intermediate **18**, we next focused on construction of the *cis*-double bond moiety (Scheme 3). Treatment of **18** with allylamine resulted in the ring opening of the lactone to give an amide. The hydroxy group of this amide intermediate was oxidized with Dess-Martin periodinane[14] to furnish ketone **19**. Attempted ring-closing metathesis of **19**, however, did not yield the desired product. Because steric repulsion between the amide side chain and the ketone moiety appeared to inhibit the approach of the two double bonds, we decided to bring these double bonds close together by connecting the nitrogen atom and the ketone moiety. While formation of an enamide from **19** via condensation between the ketone and the amide moieties could not be achieved, acid-mediated cleavage of the TBDPS group, followed by treatment with PPTS in refluxing toluene, afforded hemiaminal ether **20**. As expected, the ring-closing metathesis of **20** using the second-generation Hoveyda−Grubbs catalyst[11] proceeded smoothly to give **21** in 97% yield.

The remaining tasks primarily involved introduction of the nitrogen atom on the aromatic ring and construction of the aminal moiety. Nitration of **21** by treatment with $Cu(NO_3)_2$ in acetic anhydride proceeded smoothly. Reduction of the resulting nitro group followed by protection with an Fmoc group afforded **22**. Treatment of **22** with TMSOTf induced cleavage of the hemiaminal ether moiety to furnish, after treatment with TBAF, alcohol **23**. Oxidation of **23** followed by protection of the resulting aldehyde[15] afforded acetal **24**. Cleavage of the Fmoc group of **24** with piperidine in DMF afforded amine **25**, a known intermediate in Heathcock's racemic synthesis, which was converted to the natural product according to the published protocol.[4] Thus, reduction with $LiAlH_4$, cleavage of the ethylene acetal moiety in refluxing acetic acid, and oxidation with PDC in methylene chloride afforded (−)-isoschizogamine (**1**).

In conclusion, we have achieved the first asymmetric total synthesis of (−)-isoschizogamine. Key features of our synthesis include a facile construction of the carbon framework of the natural product using a Wagner−Meerwein rearrangement, a tandem metathesis, a stereoselective rhodium-mediated 1,4-

Scheme 3[a]



[a]Reagents and conditions: (a) allylamine, 2-pyridone, THF, 50 °C, 84%; (b) Dess-Martin periodinane, CH_2Cl_2, rt, 99%; (c) conc HCl, MeOH, 0 °C, 98%; (d) PPTS, toluene, reflux, 72%; (e) the second-generation Hoveyda−Grubbs catalyst, toluene, 70 °C, 97%; (f) $Cu(NO_3)_2{\cdot}3H_2O$, Ac_2O, CH_2Cl_2, 0 °C, 97%; (g) $NaBH_4$, $Cu(acac)_2$, EtOH, rt; (h) FmocCl, *i*-Pr_2NEt, CH_2Cl_2, 86% (2 steps); (i) TMSOTf, 2,6-lutidine, CH_2Cl_2, rt; (j) TBAF, AcOH, THF, rt, 85% (2 steps); (k) Dess-Martin periodinane, CH_2Cl_2, rt; (l) $(TMSOCH_2)_2$, TMSOTf, CH_2Cl_2, −78 °C, 96% (2 steps); (m) piperidine, DMF, rt; (n) $LiAlH_4$, THF, reflux; (o) aq AcOH, reflux; (p) PDC, CH_2Cl_2, rt, 23% (4 steps).

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addition of an arylboronic acid, and a ring-closing metathesis via hemiaminal ether **20**. The absolute configuration of natural isoschizogamine, which was determined through comparison of the observed and calculated VCD, ECD, and optical rotation,[16] has been unambiguously confirmed by our synthesis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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