Natural Product Synthesis

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An Enantioselective Total Synthesis of (−)-Isoschizogamine

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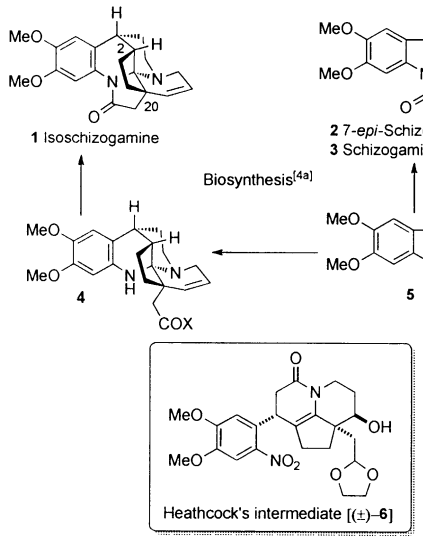
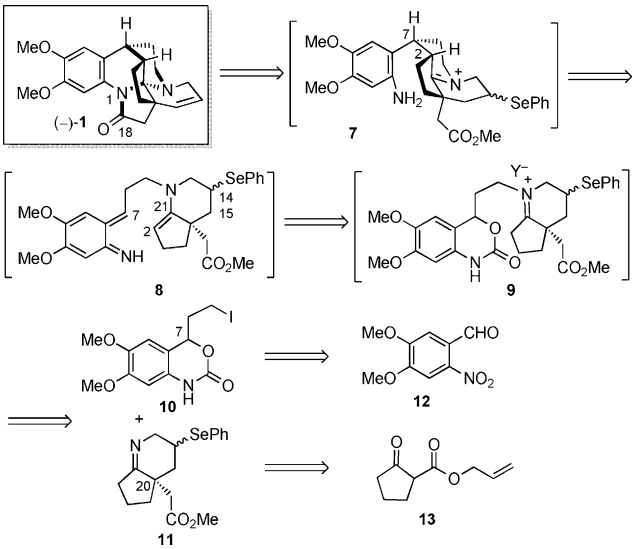
Abstract: *A concise enantioselective total synthesis of (−)-isoschizogamine, a complex bridged polycyclic monoterpene indole alkaloid, was accomplished. N-Alkylation of an enantio-enriched imine with an alkyl iodide afforded an iminium salt, which, upon heating by microwave irradiation in the presence of pivalic acid, was converted into the hexacyclic structure of natural product by a complex but ordered domino sequence. The one-pot process leading to the formation of one C−C bond and three C−N bonds created three rings and three contiguous stereogenic centers with complete control of both the relative and absolute stereochemistry.*

(−)-Isoschizogamine [(−)-**1**; Scheme 1], a highly rearranged monoterpene indole alkaloid belonging to the *Aspidosperma* subfamily,[1] was isolated from the shrub *Schizozygia caffaeoides* by Renner in 1963.[2] Originally proposed as a C7-*epi*-schizogamine (**2**),[3] its structure was revised in 1998 by Hájíček and co-workers by extensive spectroscopic studies.[4] The absolute configuration of (−)-isoschizogamine, initially determined by comparison of calculated and observed VCD, ECD, and optical rotation,[5] was later confirmed by the asymmetric total synthesis by Fukuyama and co-workers.[6] The hexacyclic framework of (−)-isoschizogamine includes a unique [6,6,6,5]diazafenestrane system[7] with an additional C2–C20 bridged five-membered ring,[8] and a densely substituted tetrahydroquinoline unit with four contiguous stereogenic centers. It was hypothesized that biosynthetically, (−)-isoschizogamine was synthesized from the aminal **4**, which is in turn derived from the pentacycle **5** by a sequence of N−C21 oxidation to iminium, aziridinium formation, and reductive opening.[4a] In contrast, direct lactamization of **5** would afford schizogamine (**3**; Scheme 1). The fascinating molecular architecture of (−)-**1** has attracted the attention of synthetic chemists and in 1999, Heathcock and co-workers reported a landmark eight-step synthesis of (±)-**1** by way of a highly convergent synthesis of the intermediate (±)-**6**. The compound (±)-**6** was subsequently converted into (±)-**1** in five steps, akin to the biosynthesis proposal.[9] This report was followed by elegant enantioselective syntheses of (−)-**1** in 2012 and 2015 by the groups of Fukuyama[6] and Qin,[10] respectively, both via intermediates similar to **6**. Other imaginative synthetic approaches have been developed by the groups of Magomedov,[11] Padwa,[12] and Tokuyama.[13] We report herein a concise asymmetric synthesis of (−)-isoschizogamine featuring a key heteroannulation reaction which leads to the formation of a hexacyclic structure in a one-pot manner.

Our retrosynthetic analysis of (−)-isoschizogamine [(−)-**1**] is outlined in Scheme 2. Disconnection of the amide and aminal functions in (−)-**1** would afford the intermediate **7**, in



Scheme 1. (−)-Isoschizogamine [(−)-**1**]: structure, biosynthesis and Heathcock's key synthetic intermediate.



Scheme 2. Synthesis design for (−)-**1**.

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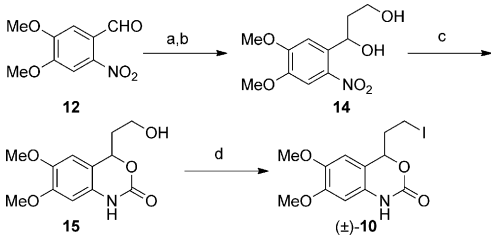
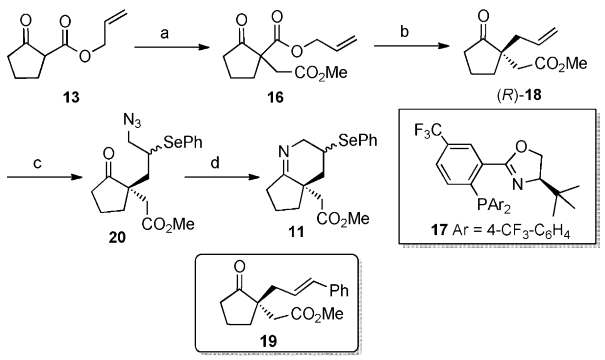
which the phenylselenide function would serve as a handle for the introduction of the C14–C15 double bond. Further cleavage of the C2–C7 bond would provide the intermediate **8** containing an enamine and transient aza-*ortho*-quinone methide function. The latter would be generated in situ by a retro-Diels–Alder reaction of the cyclic carbamate **9**,[14,15] which in turn could be obtained by alkylation of the cyclic imine **11** with iodide **10**. The iodide **10** and enantioenriched **11** could be synthesized from 6-nitroveratraldehyde (**12**) and allyl 2-oxocyclopentane-1-carboxylate (**13**), respectively. We hoped to construct the hexacyclic structure of (−)-isoschizogamine in a one-pot manner from **10** and **11**, and to control both the relative and absolute configuration of three contiguous stereogenic centers (C2, C7, C21) of the natural product through the quaternary carbon center (C20) of **11**. According to this scheme there would be no need to prepare the enantioenriched iodide **10** since its benzylic stereogenic center (C7) would be destroyed and regenerated in the process via the aza-*ortho*-quinone methide intermediate **8**.

Synthesis of the alkyl iodide (±)-**10** is shown in Scheme 3. $TiCl_4$-mediated allylation of readily available 6-nitroveratraldehyde (**12**) with allyltrimethylsilane afforded a homoallylic alcohol, which was converted into the 1,3-diol **14** by ozonolysis of the terminal olefin followed by reductive workup with $NaBH_4$.[16] Hydrogenation of **14** in the presence of diethyl pyrocarbonate gave an unstable ethyl carbamate, and upon addition of K_2CO_3 it was cyclized in situ into the 1,4-dihydro-2*H*-benzo[*d*][1,3]oxazin-2-one derivative **15** in 55% yield over three steps. Treatment of **15** with iodine and triphenylphosphine under Appel conditions provided the desired (±)-**10** in 76% yield.



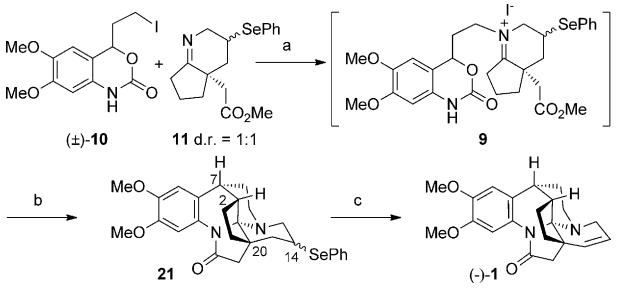
Scheme 3. Synthesis of (±)-**10**. a) TMS allyl, $TiCl_4$, CH_2Cl_2, −78 °C; b) O_3, MeOH, −78 °C; then $NaBH_4$, −78 °C to RT; c) Pd/C, H_2, $(EtOCO)_2O$, MeOH; then K_2CO_3, 55% from **12**; d) I_2, PPh_3, imidazole, CH_2Cl_2/THF (1:1), RT, 76%. THF = tetrahydrofuran, TMS = trimethylsilyl.

Synthesis of the imine **11** is shown in Scheme 4. Alkylation of allyl 2-oxocyclopentane-1-carboxylate (**13**), prepared in two steps from adipic acid by a sequence of esterification and Dieckmann condensation of the resulting diester (see the Supporting Information), with methyl bromoacetate afforded **16** in 95% yield. Asymmetric decarboxylative allylation of **16** under the Stoltz conditions using (*R*)-(*p*-CF_3)$_3$-*t*BuPHOX (**17**), as a ligand, afforded (*R*)-**18** in 90% yield with 83% *ee*.[17] With (*R*)-*t*BuPHOX as ligand under otherwise identical conditions, the desired (*R*)-**18** was isolated with only 60% *ee*.[18] The *ee* value of **18** was determined by SFC analysis of its UV-active derivative **19**. The absolute configuration of **18** was assigned based on literature precedents[17,18] and was further confirmed by its conversion into (−)-isoschizogamine. Azidophenylselenenylation of the terminal double bond[19] in (*R*)-**18** under oxidative conditions regioselectively afforded the desired alkyl azide **20** as a mixture of two diastereomers (d.r. = 1:1). The lack of diastereoselectivity in this alkene difunctionalization reaction was of no consequence since the newly created chiral center will become an sp^2-hybridized carbon atom upon elimination of phenylselenyl substituent. Staudinger reduction **20** (Me_3P in THF) afforded a phosphazene intermediate which underwent in situ intramolecular aza-Wittig reaction to provide **11** in 89% yield.



Scheme 4. Synthesis of the enantioenriched imine **11**. a) Methyl bromoacetate, K_2CO_3, acetone, 50 °C, 95%; b) [$Pd_2(dba)_3$], ligand **17**, toluene, 60 °C, yield: 90%, 83% *ee*; c) $(PhSe)_2$, NaN_3, $PhI(OAc)_2$, CH_2Cl_2, 72%, d.r. = 1:1; d) Me_3P, THF, RT, 89%. dba = dibenzylideneacetone.

With the desired coupling partners in hand, the heteroannulation of **10** and **11** was examined (Scheme 5). After much experimentation, it was found that heating a solution of **10** and **11** [1.2 equiv in CH_3CN (0.5 M), microwave irradiation] for 1 hour afforded cleanly the desired iminium salt **9**. After removal of acetonitrile, the crude **9** and an excess of pivalic acid (20.0 equiv) was dissolved in 1,2-dichloroethane/1,2-dichlorobenzene (1:3, $c = 0.025$ M). The resulting solution was heated to 160 °C for 30 minutes under microwave irradiation. Under these optimized reaction conditions, the desired hexacyclic compound **21** was isolated in 45% yield as a mixture of two diastereomers (d.r. = 1:1) with the desired

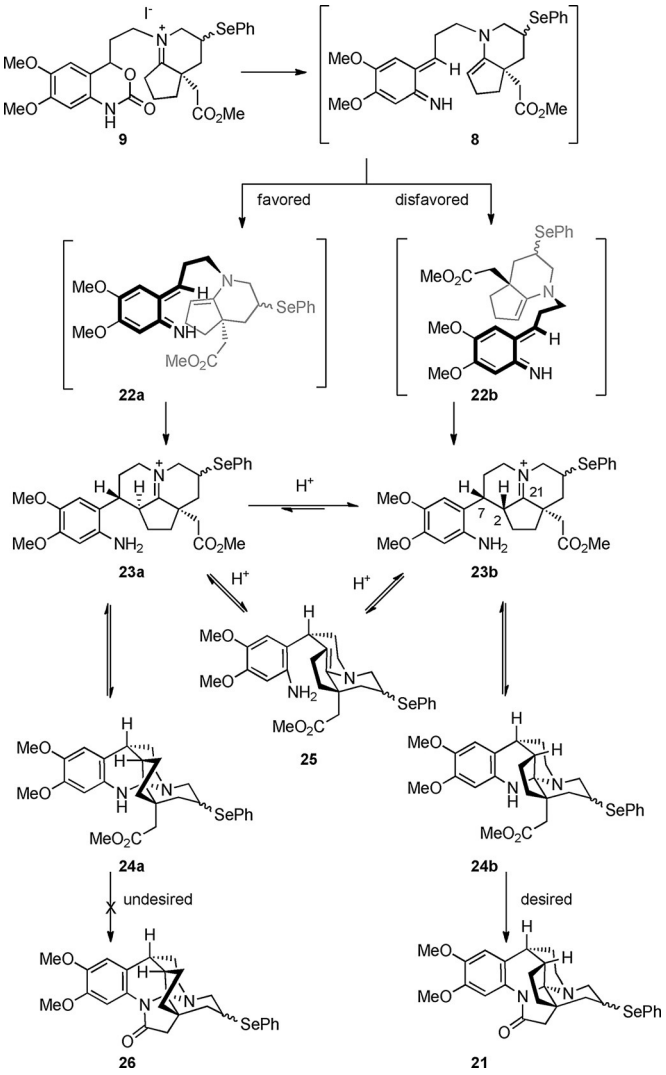


Scheme 5. Total synthesis of (−)-**1**. a) CH_3CN ($c = 0.5$ M), 100 °C (microwave); b) 1,2-dichloroethane/1,2-dichlorobenzene (1:3, $c = 0.025$ M), PivOH, 160 °C (microwave), 45%; c) $NaIO_4$, $NaHCO_3$, MeOH; then $Na_2S_2O_3$, Et_2NH, 1,2-dichloroethane, 55 °C, 2.5 h, 46%.

relative and absolute configurations at C2, C7, and C21. The presence of an acid additive is essential to ensure a reproducible yield of **21**. Among a variety of Lewis acids ($AgBF_4$, Al_2O_3) and Brønsted acids (TFA, HOAc, $ClCH_2COOH$, $Cl_2CHCOOH$, PhCOOH, *t*BuCOOH) examined, pivalic acid gave the best results. The two C14 epimers of **21** were separable and were fully characterized. However, a mixture of two epimers was used for the next step for the sake of convenience. Oxidation of **21** to the selenoxide ($NaIO_4$ in methanol buffered with aqueous $NaHCO_3$),[20] followed by a *syn* elimination in MeOH/1,2-dichloroethane in the presence of $Na_2S_2O_3$ and diethyl amine, afforded (−)-isoschizogamine [(−)-**1**] as the only isolable product in 46% yield. We note here that natural product (−)-**1** with the double bond distal to the nitrogen atom was the only regioisomer isolated from the reaction mixture.[21] The physical and spectroscopic data of the synthetic (−)-isoschizogamine were identical to those reported for the natural product. We have also synthesized (±)-isoschizogamine following the same synthetic scheme. The specific optical rotation value of the synthetic (−)-isoschizogamine {$[\alpha]_D = -193$, $c = 0.135$, $CHCl_3$} was consistent with its enantiomeric purity (83% *ee*).

The annulation of **10** and **11** leading to **21** created three rings by formation of one C–C bond and three C–N bonds. Three contiguous stereogenic centers were created with high diastereoselectivity. A possible reaction pathway accounting for the observed stereoselectivity is depicted in Scheme 6. Cycloreversion of **9** would produce the *trans*-azadiene **8**. Although intramolecular [4+2] cycloadditions between in situ generated aza-*ortho*-quinone methide and electron-rich olefins leading to fused bicycles are known,[14,15] the same reaction leading to bridged ring system is, to the best of our knowledge, unprecedented. Indeed, with a three-carbon tether between the diene and dienophile (see **8**), the intramolecular Diels–Alder reaction generally affords fused rather than bridged ring systems. Therefore, we assumed that the subsequent transformation proceeded through a stepwise process. The cyclization of **8** could proceed through two possible transition states, **22a** and **22b**, which would afford the imines **23a** and **23b**, and finally **24a** and **24b**, respectively. The transition state **22a** with the CH_2CO_2Me side-chain pointing away from the aromatic ring should in principle be favored over alternative transition state **22b**, thus producing **23a** and eventually **24a** with undesired configuration at C2. However, based on Heathcock's earlier observation,[9a] it is reasonable to assume that **24b** is thermodynamically more stable than **24a**, and that the undesired **24a** can be converted into **24b** under acidic conditions via intermediate **25** by way of iminium–enamine tautomerization. Therefore, we hypothesized that the preferential formation of **24b** over **24a** was under thermodynamic control. A faster lactamization of **24b** over that of **24a** could drive the preferential formation of the observed hexacyclic compound **21**.[22]

In conclusion, an enantioselective total synthesis of (−)-isoschizogamine has been accomplished in seven steps in the longest linear sequence with 11.3% overall yield from 2-oxocyclopentane-1-carboxylate (**13**) or in nine steps from adipic acid with 8.2% overall yield. By simply heating a solution of two easily available building blocks, a racemic alkyl iodide [(±)-**10**] and an enantioenriched bicyclic imine (**11**), a hexacyclic core of the alkaloid was formed with concurrent generation of three rings and three contiguous stereogenic centers with complete control of relative and absolute stereochemistry.[23]



Scheme 6. Stereochemical course of the cyclization process.

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