Total Synthesis of (±)-Isoschizogamine

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ABSTRACT



Isoschizogamine has been prepared for the first time. The synthesis requires eight steps from a readily available ketone starting material and features an aminal-forming cyclization that is based on a proposed biosynthetic transformation.

Isoschizogamine (1), a member of the schizozygane family of indole alkaloids, was recently isolated by Hajicek and coworkers from the shrub *Schizozygia caffaeoides*.^{1,2} Its structure, which differs from the ring system typically found in the schizozygane alkaloids (e.g., 2),³ was elucidated by NMR techniques. The most striking difference is the presence of the aminal motif. Hajicek and co-workers proposed a partial biosynthesis to explain the formation of the unusual, aminal-containing hexacyclic ring system from an intermediate with the more typical schizozygane skeleton, 2 (Scheme 1). Attack of the indoline nitrogen on the immonium carbon



would lead to the aziridinium intermediate **3**, which might be opened reductively and the lactam ring closed to provide isoschizogamine (**1**).

We saw the novel structure of isoschizogamine as an interesting synthetic target and thought that we might be able

to mimic the proposed biosynthetic formation of the aminal function by modification of compounds we had previously employed for our total synthesis of vallesamidine.⁴ In the vallesamidine synthesis, lactam **5** was prepared in four steps from 2-ethylcyclopentanone (Scheme 2). It can be seen that



protonation of the enamide double bond in 5 would give an acyl immonium species that is similar to intermediate 2 in

⁽¹⁾ Hájícek, J.; Taimr, J.; Budesínsky, M. Tetrahedron Lett. 1998, 39, 505.

⁽²⁾ Renner, U. Lloydia 1964, 27, 406.

⁽³⁾ Kompis, I.; Hesse, M.; Schmid, H. Lloydia 1971, 34, 269.

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the proposed biosynthesis. The only major difference between the ring system in such an acyl immonium intermediate and biosynthetic intermediate 2 is that the five-membered indoline ring is closed in 2. Addition of the aniline nitrogen in 5 to the immonium carbon formed by protonation of the enamide double bond would yield the isoschizogamine framework.

This idea was used to model a key transformation in the total synthesis of isoschizogamine. Because enamide **5** did not undergo the desired cyclization, it was reduced with lithium aluminum hydride to tertiary enamine **6**. Upon workup,⁵ enamine **6** was protonated to give immonium ion **7**, which cyclized to form diastereomeric aminals **8** and **9**. The formation of the two observed diastereomers can be explained by protonation of the two diastereotopic faces of the double bond in enamine **6**. The stereochemistry indicated in structure **8** was established by single-crystal X-ray diffraction. Treatment of either isomer with acetic acid resulted in an 85:15 ratio of **8** to **9**.

With confidence that the basic aminal-forming reaction would work, we set out to prepare isoschizogamine via an appropriately functionalized version of lactam **5** such as **10** (Scheme 3). Lactam **10** was envisioned as coming from the



Michael addition of the enamine tautomer of imine **12** to cinnamic acid **11** in a reaction similar to that used in our vallesamidine synthesis.⁴

As shown in Scheme 4, the thermodynamic enolate of the readily available ketone 13^6 was allowed to react with

3-azidopropanal⁷ in an aldol reaction. There is disagreement in the literature as to whether 2-substituted cyclopentanones can be deprotonted regioselectivly at the more substituted α -position.⁸ However, it was found that the thermodynamic enolate could be formed with high selectivity by slowly adding a slight excess of KHMDS to 13 over 2 h. To obtain high regioselectivity and diastereoselectivity in the aldol reaction, the enolate of a metal other than potassium was needed. Consequently, a number of Lewis acids were examined for trapping the potassium enolate. Eventually we found that treatment of the potassium enolate with Bu₂BOTf and subsequent aldol reaction gave exclusively syn aldol 14. The use of i-Bu₂AlCl gave a slightly higher yield of adduct 14, but with this Lewis acid there was produced a mixture of diastereomers that was difficult to separate. Hydrogenation of the azide group in aldol 14 gave imine 12.

Unfortunately, the Michael addition reaction of imine 12 to α,β -unsaturated acid **11** which was directly analogous to that used in our vallesamidine synthesis (Scheme 3) gave none of the desired product. Changing the Michael acceptor to the acid chloride,^{9,10} azide,^{9,11} anhydride,⁹ and ester also all failed to give the desired addition-cyclization product. We then turned our attention to α,β -unsaturated dicarbonyl compounds as the Michael acceptors in this reaction. A search of the literature indicated that Meldrum's acid derivatives of aldehydes such as 16 (Scheme 5) were excellent Michael acceptors and also had the advantage that the adducts formed from the Michael addition to these substrates could serve as good acylating agents.¹² Thus, α , β unsaturated diester 16 was prepared by Knovenagel condensation of 2-nitroveratraldehyde with Meldrum's acid (Scheme 5). We then utilized this Michael acceptor in our imine addition-cyclization reaction. Imine 12 underwent Michael addition to 16 at -40 °C to give an intermediate which, upon heating, underwent cyclization with concomitant loss of acetone and carbon dioxide, providing a mixture of diastereomeric lactams 17 and 18 in a ratio of 88:12 and a total yield of 74% from aldol 14. Dehydration of 17 with Martin's sulfurane¹³ gave alkene **19**.

The reduction-cyclization sequence was carried out under conditions similar to those used in the model system (Scheme 2). The aromatic nitro group in lactam **19** was first reduced using NaBH₄ and catalytic Cu(acac)₂¹⁴ (Scheme 6) to give compound **20**. The air and acid sensitivity of **20** made it







difficult to handle and purify so it was used without purification in the next step. The lactam carbonyl was reduced with LiAlH₄, which upon workup gave aminal **21** as a single diastereomer. Treatment of this aminal with acetic acid and water under conditions insufficient to hydrolyze the dioxolane acetal gave a 3:7 ratio of diastereomer **21** to **22**. The stereochemistry was determined in these cases by comparison of the ¹H NMR spectra of **21** and **22** to the spectra of aminals **8** and **9**.

Treatment of **21** with aqueous acetic acid under more forcing conditions provided hemiaminal **23** (Scheme 7). This



crude product was then oxidized with pyridinium dichromate¹⁵ to give (\pm) -isoschizogamine (1) in 27% yield for the four steps from 19. None of the other possible diastereomer was observed in the NMR spectrum of the crude oxidation product.

In summary, isoschizogamine was prepared from ketone 13 in eight steps and 7% overall yield.

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Supporting Information Available: Experimental procedures and full characterization for compounds **8**, **9**, **12**, **14–19**, and **1**; ¹H NMR spectra for compounds **8**, **9**, and **1**; ¹³C NMR spectrum for compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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