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Natural Products

# A Photoinduced Cyclization Cascade—Total Synthesis of (−)-Leuconoxine

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*In memory of Prof. Dr. rer. nat. Dr. h. c. Ekkehard Winterfeldt*

**Abstract:** A protecting-group-free and enantioselective total synthesis of the monoterpenoid indole alkaloid (−)-leuconoxine was accomplished. The key step comprises a novel photoinduced domino macrocyclization/transannular cyclization involving the Witkop cyclization, for which additional mechanistic evidence is provided. This process furnishes a diaza[5.5.6.6]fenestrane skeleton, which is a hitherto unprecedented structure element.

The plant family *Apocynaceae* produces a broad spectrum of biologically active monoterpenoid indole alkaloids.[1] Among them, the leuconolam–leuconoxine–mersicarpine alkaloid family has been isolated from several *Apocynaceae* species.[2–4] It has immediately drawn significant attention from the synthetic community, which is reflected by four completed total syntheses in the last two years.[5] Leuconoxine (**1**) is characterized by its signature structure element, a hitherto completely unprecedented diaza[5.5.6.6]fenestrane system **2**,[6] consisting of the ABCD rings (Figure 1). In comparison with the completed syntheses, our retrosynthetic planning involves a cyclization cascade of linear precursor **4**, which forms three of the four rings of the fenestrane in a single chemical transformation to give compound **3**.

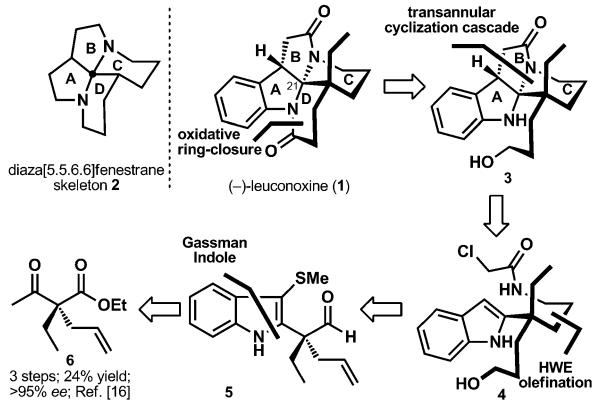


**Figure 1.** Retrosynthetic analysis for leuconoxine (**1**).

Besides leuconoxine and its structural siblings leuconodines A–F[7] and melodinine E,[8] the fenestrane structure motif is only reported in three other natural products: laurenene,[9] the penifulvins such as penifulvin A,[10] and asperaculin A[11]—all of them are terpenes. To the best of our knowledge, the leuconoxine subgroup represent the first alkaloids containing a fenestrane structure motif. This exceptional feature prompted us to engage in their total synthesis to develop an elegant and concise access to this intriguing diazafenestrane system **2**.

Structure analysis of leuconoxine (**1**) revealed two major synthetic challenges: 1) A stereogenic quaternary carbon center; and 2) the central diazaspiro aminal center C-21 (Figure 1). With these constraints, we turned our attention to a photochemical reaction for the formation of the ABC-ring system—the Witkop cyclization.[12] This reaction constitutes a photochemical C–H activation avoiding prefunctionalization of the molecule and facilitating a protecting-group-free synthesis.[13] As shown in Figure 1, we started our retrosynthetic analysis by disconnection of ring D. This leads to compound **3**, which harbors the ABC ring system of the natural product. A photochemical induced Witkop-/transannular cyclization cascade of amide **4** in a single step then affords the tricyclic ABC ring system of **3**. The Gassman protocol[14] was chosen for the synthesis of 2-substituted indole **5**. The chiral quaternary carbon center is obtained from known β-ketoester **6**, which can be prepared in three steps from commercially available ethyl 2-ethylacetoacetate following Suemune's protocol.[15]

Our total synthesis commenced with the preparation of β-ketosulfide **7**, which is required for Gassman indole synthesis. For this purpose, methyl ketone **6** was first converted to the corresponding bromoketone, which was then refluxed in $SMe_2$ to provide **7** in 90% yield. Gratifyingly, exposure of sulfide **7** to *N*-chloroaniline at −45 °C, followed by $NEt_3$ treatment and acidic work-up, afforded the 3-(methylthio)indole **8** in 77% yield (Scheme 1). With indole **8** in hand, preparation of the requisite α-chloroacetamide moiety for Witkop cyclization was now envisioned. Since standard desulfurization with Ra-Ni led to complex product mixtures, selective removal of the sulfide group in the presence of the allyl double bond was accomplished in 88% yield using thiosalicylic acid in TFA.[16] Elongation of the tether-chain was accomplished through a three-step sequence involving DIBAL-H reduction, Parikh-Doering oxidation, and Wittig olefination to generate α,β-unsaturated ni-

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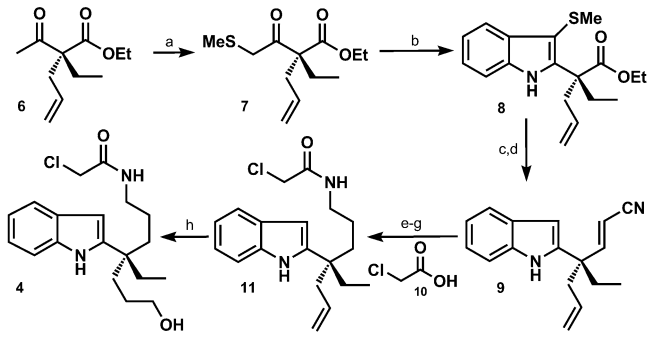
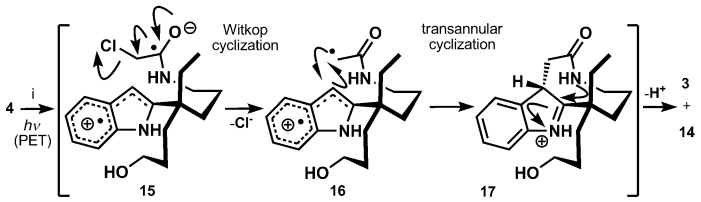


**Scheme 1.** Preparation of the Witkop cyclization precursor. Reagents and conditions: a) $NEt_3$, TMSOTf, $CH_2Cl_2$; NBS, THF; $SMe_2$, toluene, 80 °C, 90%; b) aniline, −45 °C, $CH_2Cl_2$, MeCN, *t*BuOCl, then $NEt_3$, then $H_3PO_4$, 77%; c) TFA, thiosalicylic acid, 88%; d) DIBAL-H; DMSO, $SO_3$·pyr; $Ph_3P$=CHCN, toluene, 80 °C, 73% (3 steps); e) Mg, MeOH, 85%; f) $LiAlH_4$, $Et_2O$; g) **10**, DIC, DMAP, 73% (2 steps); h) $BH_3$·$SMe_2$, THF, then $NaBO_3$, 51%. NBS = *N*-bromosuccinimide, TFA = trifluoroacetic acid, DIBAL-H = diisobutylaluminium hydride, DIC = *N*,*N*′-diisopropylcarbodiimide, DMAP = 4-dimethylaminopyridine.

trile **9** in 73% yield. Reduction of **9** using Mg/MeOH (85% yield), followed by LAH yielded the corresponding amine, which was trapped in situ with 2-chloroacetic acid (**10**) to give α-chloroacetamide **11** in 73% yield over two steps. Finally, a sequence of hydroboration–oxidation afforded linear Witkop precursor **4** in 17% overall yield starting from known **6**. This synthetic route was routinely carried out on multigram scale and requires only six chromatographic purifications.

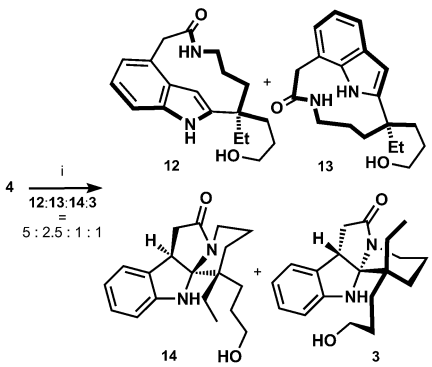
Having established an efficient route to precursor **4**, we started to explore the proposed Witkop photocyclization. Since 2-substituted indoles preferentially cyclize to the 3-position yielding 2,3-annulated products, we expected that irradiation of **4** at 254 nm would generate this C–C-bond. To our surprise, we obtained (2,4)indolophane **12** and (2,7)indolophane **13** as the major products instead, resulting from cyclization to the C4- and C7-indole positions (Scheme 2). Additionally, two minor products were formed in 10% combined yield. Careful structure elucidation of these two products revealed structures **14** and **3**, which are diastereomers and were obtained in a 1:1 ratio. In accordance with the accepted mechanism of the Witkop reaction, the domino sequence is initiated by a photoinduced electron transfer (PET) from the excited state of the indole chromophore to the chlorocarbonyl moiety generating intermediate **15** (Scheme 3). Loss of a chloride anion leads to diradical cation **16**, which undergoes cyclization with the aromatic ring to yield cation **17**. Instead of rearomatization of **17**, transannular iminium ion trapping occurs, affording advanced intermediate **3**. In this way, for the first time we are able to provide experimental evidence for the proposed iminium ion **17** as an intermediate in the Witkop cyclization. The development of this domino macrocyclization/transannular cyclization yields three of the four rings of the diaza[5.5.6.6]fenestrane system along with the sensitive aminal functionality.

To improve the diastereoselectivity in favor of **3**, we protected the hydroxyl group of **4** with bulky silyl groups such as TBDPS or TIPS. Interestingly, this changed the ratio of **14** and **3** in favor of the undesired isomer (**14**:**3** = 1.4–1.5:1). Assuming that solvents with high dielectric constant might beneficially

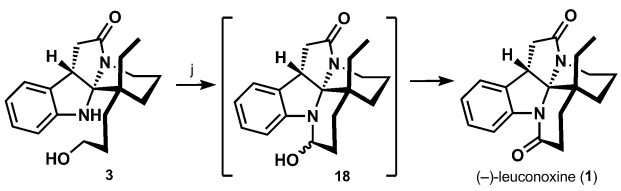


**Scheme 3.** Proposed mechanism of the domino cyclization sequence.

stabilize the charged intermediates involved in the reaction, we also examined aqueous methanol and acetonitrile based solvent systems. These conditions gave comparable ratios of the domino reaction products **14** and **3**, yet with decreased overall yield. Furthermore, the use of sodium carbonate as base proved to be crucial, since the reaction in the presence of lithium carbonate exclusively afforded the two eleven-membered ring indolophanes **12** and **13**. Of the two diastereomers formed in this process, only **3** can undergo final δ-lactam formation. With reasonable amounts of **3** in hand, we thus oxidized the hydroxyl group with TPAP/NMO to give aminal **18**, thereby closing ring D and establishing the fenestrane system, which upon second oxidation in situ furnished (−)-leuconoxine (**1**) in 50% yield (Scheme 4). The spectroscopic data were identical to those reported in the literature [3, 5].



**Scheme 2.** Products of the Witkop cyclization of **4**. Reagents and conditions: i) *hν* (254 nm), $Na_2CO_3$, MeOH, rt, 49%.



**Scheme 4.** Total synthesis of (−)-leuconoxine (**1**). Reagents and conditions: j) TPAP, NMO, MeCN, 50%. TPAP = tetrapropylammonium perruthenate, NMO = *N*-methylmorpholine *N*-oxide.

In conclusion, we have accomplished a concise, enantioselective total synthesis of (−)-leuconoxine in only eight isolated steps from known β-ketoester **6** without the requirement of protecting groups, albeit in low yields for the photo-reaction, and an overall yield of 0.5%. Our synthesis features a photoinduced domino macrocyclization/transannular cyclization process, which constructs three of the four rings of the diaza[5.5.6.6]fenestrane skeleton in one single operation. The fenestrane scaffold is unprecedented, and therefore our method provides a direct and mild access to this signature structure element.

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**Keywords:** fenestrane · indole alkaloid · total synthesis · transannular cylization · witkop photocyclization

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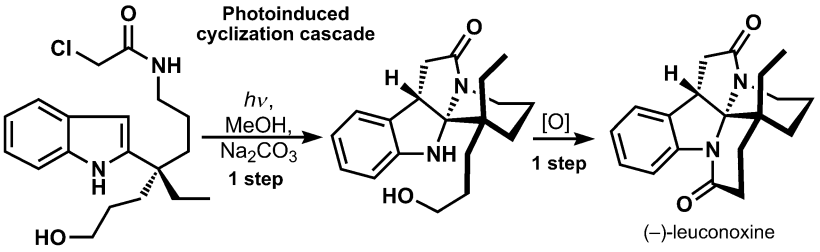
**A Photoinduced Cyclization Cascade—Total Synthesis of (−)-Leuconoxine**




**A signature structure element**: A photoinduced domino macrocyclization/transannular cyclization was developed for the enantioselective and protecting-group-free total synthesis of the monoterpenoid indole alkaloid (−)-leuconoxine. This process furnishes the unprecedented diaza[5.5.6.6]fenestrane structure element from a simple, linear precursor in two chemical transformations, also providing additional evidence for the proposed mechanism of the Witkop cyclization.