Natural Product Synthesis

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Enantioselective Total Synthesis of the *Melodinus* Alkaloid (+)-Meloscine**

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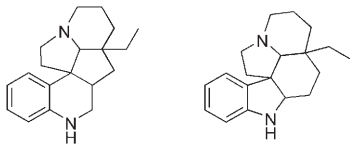
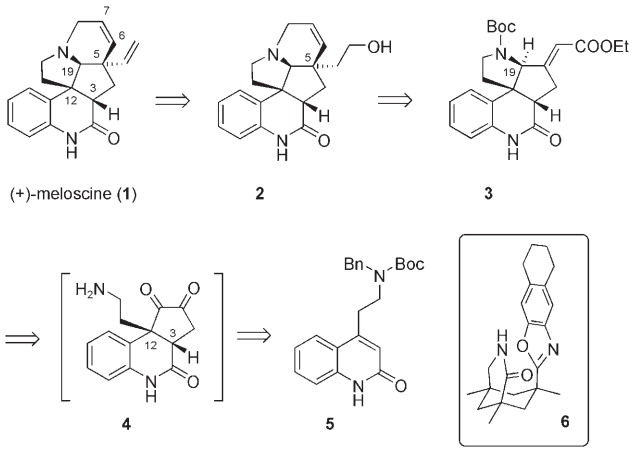
Dedicated to Professor Gernot Boche on the occasion of his 70th birthday

Melodinus alkaloids, also known as meloquinolines, represent a group of monoterpenoid indole alkaloids. Their pentacyclic carbon skeleton **A** is closely related to the general structure **B** of *aspidoperma* alkaloids of the aspidospermidine type.[1]



Melodinus alkaloids were isolated from certain *Apocynacea* species, for example, from *Melodinus scandens* Forst.[2] and from *Melodinus hemsleyanus* Diels.,[3] which play a role in traditional Chinese folk medicine. A proposed biosynthetic pathway **B**→**A** proceeding by skeletal rearrangement appears to be likely as it has been realized in small yields by laboratory syntheses.[4]

The prototype of all *Melodinus* alkaloids is (+)-meloscine (Scheme 1), the constitution and absolute configuration of which were elucidated already in 1969 by Bernauer et al.[5] and Oberhänsli.[6] From a synthetic point of view, the construction of the central, highly substituted cyclopentane ring with four stereogenic centers, two of which are quaternary, represents the main challenge, which only Overman et al. have successfully mastered so far.[7] Starting from ethyl-2-oxocyclopentylacetic acid, they achieved the synthesis of racemic (±)-meloscine in 25 steps with an overall yield of 2%. However, neither the synthesis of enantiopure (+)-meloscine nor an enantiospecific entry into the meloquinoline skeleton has yet been described.[8] We report herein on the first enantioselective total synthesis of (+)-meloscine, which employs a template-controlled [2+2] photocycloaddition as one of the key steps.[9]



Scheme 1. Retrosynthetic analysis of (+)-meloscine. Boc = *tert*-butyloxycarbonyl, Bn = benzyl.

Retrosynthetic disconnection of the natural product led us from intermediate **2**, which had already been used in racemic form by Overman et al., to the tetracyclic ester **3**, which offered a variety of possibilities for the construction of the quaternary stereogenic center at C5.[10] The plan to construct the stereogentic center at C19 by reductive amination and to introduce the exocyclic double bond by a carbonyl olefination resulted in the hypothetical 1,2-diketone **4** as a formal intermediate, which was to be derived from a [2+2] photocycloaddition product of the known quinolone **5**.[11] In fact, an enantioselective [2+2] photocycloaddition in the presence of the chiral complexing agent **6**[12] was considered as the pivotal step for the generation of the stereogenic centers at positions C3 and C12.

Ring expansion from the four- to the five-membered ring, however, was not trivial, and numerous attempts to construct a cyclopentane ring by a classical Wagner–Meerwein rearrangement of an iminium ion[13] were futile. Considering these difficulties, the two-step sequence depicted in Scheme 2 was a decisive breakthrough, as it allowed for the rapid synthesis of an equivalent of aminodiketone **4** in a surprisingly easy fashion. The rearrangement of cyclobutane **7** into the α-hydroxycyclopentenone **9** can be explained as a retro-benzilic ester rearrangement[14] (step b), which effectively takes advantage of a captodative electronic situation in the electron-rich alkoxide **8**. The silyl enol ether[15] derived from methyl pyruvate was employed for the first time in a [2+2] photocycloaddition and gave the cycloaddition product **7** (step a) with perfect regio- and diastereoselectivity.

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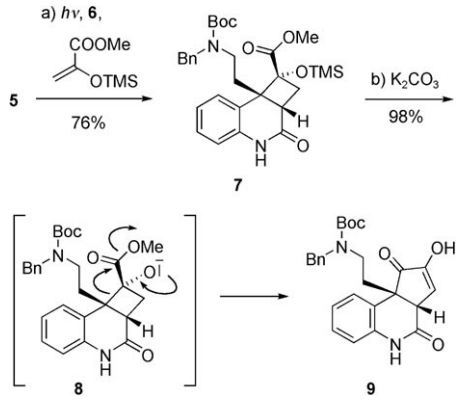
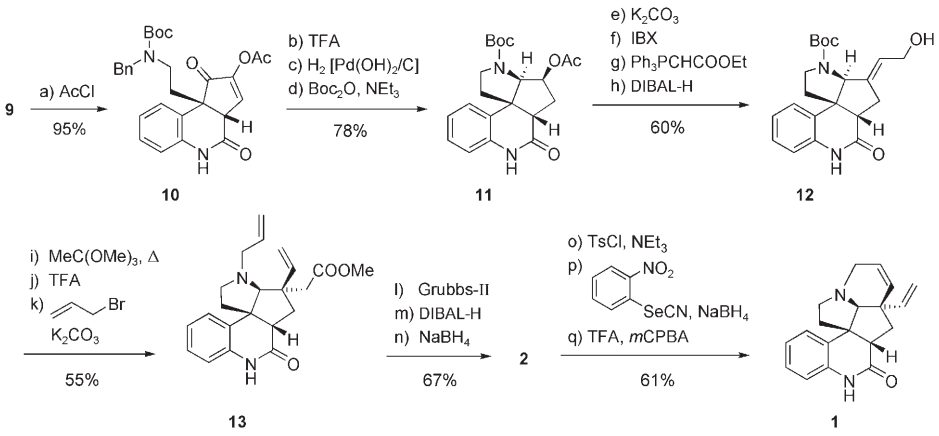


Scheme 2. Synthesis of the tricyclic intermediate **9** by a sequence of enantioselective [2+2] photocycloaddition and rearrangement: a) *hν* (370 nm), **6** (2.5 equiv), silyl enol ether (5.0 equiv), toluene, −60 °C, 4 h, 76%; b) K_2CO_3, MeOH, 20 °C, 2 h, 98%.

Successful further conversion of α-hydroxycyclopentenone **9** required chemical fixation in its enol form, which was achieved by conversion to its *O*-acetyl derivative **10** (Scheme 3). After cleavage of the Boc group, heterogeneous reduction with Pearlman's catalyst $Pd(OH)_2/C$ and hydrogen initiated a domino reaction,[16] in the course of which the C=C bond was diastereoselectively hydrogenated, the *N*-benzyl protecting group was cleaved, and the resulting free primary amine was involved in an intramolecular, diastereoselective reductive amination. As no isolation of the intermediates was necessary, the final product of this reductive sequence, *N*-Boc pyrrolidine **11**, was obtained after reprotection of the basic amine nitrogen atom in an overall yield of 78% over three steps starting from enol acetate **10**.

Pyrrolidine **11** was then converted into the Michael acceptor **3** (Scheme 1) by saponification of the acetate, oxidation of the secondary alcohol to the ketone with *o*-iodoxybenzoic acid (IBX),[17] and subsequent Wittig reaction. Unfortunately, all attempts to achieve a nucleophilic attack at the prostereogenic β-carbon atom were unsuccessful, both as intra- and as intermolecular variants. Two of the most promising options explored, radical addition reactions[18] and the addition of soft nucleophiles,[19] did not give any useful products. A solution was eventually found by conducting a Claisen rearrangement[20] of allylic alcohol **12**, which was easily accessible from ester **3** by reduction. The rearrangement was performed as the Johnson variant[21] employing trimethyl orthoacetate as the reagent. The rearrangement product was obtained as an inseparable mixture of diastereoisomers in a diastereomeric ratio (d.r.) of 70:30, with the major diastereoisomer possessing the desired relative configuration. After N-deprotection and basic workup the minor diastereoisomer spontaneously cyclized to a pentacyclic lactam which could be removed easily. N-allylation of the major diastereomer resulted in the diastereomerically pure compound **13** in 65% yield. Ring-closing metathesis[22] of **13** with a commercially available 2nd generation Grubbs catalyst[23] gave rise to the final tetrahydropyridine ring (95% yield), thus completing the construction of the pentacyclic meloquinoline skeleton. Reduction of the ester side chain was best achieved in two steps via the corresponding aldehyde and resulted in alcohol **2**, already known in racemic form. The subsequent elimination was conducted following essentially Overman's procedure.[7] In contrast to this precedence, however, the successful oxidative elimination of the intermediate selenide[24] was possible only after quantitative protonation of the basic tertiary amine by a slight excess of acid. Direct oxidation with *meta*-chloroperoxybenzoic acid (*m*CPBA) gave either no significant conversion or resulted in an unspecific decomposition if an excess of more than two equivalents of *m*CPBA was employed. (+)-Meloscine obtained after successful elimination was in every respect identical to the natural product.[4b,5,25]



Scheme 3. Completion of the total synthesis of (+)-meloscine (**1**) starting from tricyclic ketone **9**: a) AcCl (1.1 equiv), NEt_3 (1.5 equiv), THF, 0 °C, 15 min, 95%; b) TFA (10 vol%), CH_2Cl_2, 20 °C, 1 h; c) H_2 (1 atm), 15% $Pd(OH)_2/C$ (20 mol%), MeOH, 0 °C→20 °C, 18 h; d) addition of NEt_3 to pH 8–10, Boc_2O (1.3 equiv), CH_2Cl_2, 20 °C, 1 h, 78% over 3 steps; e) K_2CO_3, MeOH, 20 °C, 3.5 h, 94%; f) IBX (3.0 equiv), DMSO, 20 °C, 18 h, 94%; g) $Ph_3PCHCOOEt$ (1.4 equiv), THF, reflux, 22 h, 84%; h) DIBAL-H (3.75 equiv), CH_2Cl_2, −45 °C, 30 min, 81%; i) $MeC(OMe)_3$ (3 equiv), hydroquinone (0.66 equiv), 135 °C, 16 h, 85% (d.r. 70:30); j) TFA (10 vol%), CH_2Cl_2, 20 °C, 1 h; k) allylbromide (0.8 equiv), K_2CO_3 (1.0 equiv), MeCN, 20 °C, 20 h, 65% over 2 steps; l) Grubbs II (15 mol%), toluene, 65 °C, 18 h, 95%; m) DIBAL-H (2.1 equiv), CH_2Cl_2, −78 °C, 30 min; n) $NaBH_4$ (1.2 equiv), EtOH, 0 °C, 20 min, 70% over 2 steps; o) TsCl (10 equiv), NEt_3 (20 equiv), CH_2Cl_2, 20 °C, 18 h, 72%; p) 2-nitrophenylselenocyanate (21 equiv), $NaBH_4$ (20 equiv), EtOH, 20 °C, 80 h, 98%; q) TFA (1.5 equiv), 75% *m*CPBA (1.0 equiv), CH_2Cl_2, −78 °C to 20 °C, 4 h, 86%. AcCl = acetyl chloride, TFA = trifluoroacetic acid, DIBAL-H = diisobutylaluminum hydride, Grubbs II = benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium, TsCl = *p*-toluenesulfonyl chloride.

In conclusion, the synthesis of enantiopure (+)-meloscine (**1**) was realized starting from quinolone **5** in 15 steps and 7% overall yield. The scale of the enantioselective synthesis is still somewhat limited owing to the restricted

availability of the chiral complexing agent **6**. Generally, however, the yields of the photochemical key step are high and suitable for use on a larger scale, as could be shown in a parallel synthesis of racemic (±)-meloscine. Further conversion of the racemic photoproduct with the established methods gave access to the complete meloquinoline skeleton in multigram amounts.

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