DOI: 10.1002/chem.200802383

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Total Synthesis of Meloscine by a [2+2]-Photocycloaddition/Ring-Expansion Route

Philipp Selig,[a] Eberhardt Herdtweck,[b] and Thorsten Bach*[a]

Abstract: The unusual monoterpenoid indole alkaloid meloscine was synthesized starting from a protected aminoethylquinolone in 15 steps and an overall yield of 9%, employing a [2+2]-photocycloaddition as the stereochemistry defining key step. After the initial plan of a Wagner–Meerwein type rearrangement of a [4.2.0]- into a [3.3.0]-bicyclic substructure could not be realized, the required ring enlargement of a cyclobutane was eventually achieved by a *retro*-benzilic acid rearrangement. Generation of the central pyrrolidine ring was possible by a three-step reductive amination domino sequence. The final ring was built up by a ring-closing metathesis after the last quaternary stereocenter had been constructed by a Johnson–Claisen rearrangement. The synthesis was concluded by a selenylation–elimination sequence to build up the exocyclic vinyl group of meloscine. Using our methodology for enantioselective [2+2]-photocycloaddition mediated by a chiral complexation agent, the experimentally very simple synthesis could be performed in an enantioselective fashion (7% overall yield). The enantioselective synthesis of (+)-meloscine represents the first example of a natural product synthesis employing an enantioselective [2+2]-photocycloaddition as its key step, and illustrates nicely the synthetic potential of photochemical transformations for the construction of complex heterocyclic structures.

Keywords: asymmetric synthesis · natural products · photochemistry · rearrangement · total synthesis

Introduction

The pentacyclic alkaloid (+)-meloscine [(+)-**1**, Figure 1] represents the prototype of a small group of monoterpenoid indole alkaloids commonly referred to as *Melodinus* alkaloids or meloquinolines due to their exclusive occurrence in the *Apocynacea* species *Melodinus* ssp.[1] As their distinct structural feature the *Melodinus* alkaloids incorporate a six-membered quinolone ring within a monoterpenoid *Aspidosperma* carbon skeleton, which is derived from the typical structure of related indole alkaloids by the expansion of ring B with a concomitant contraction of ring C. This structural relationship, which most probably also represents the biogenetic origin of the *Melodinus* alkaloids is maybe best illustrated by comparison of (+)-scandine [(+)-**2**] with its indole counterpart (−)-tabersonine [(−)-**3**], an alkaloid also present in various *Melodinus* species (Figure 1).

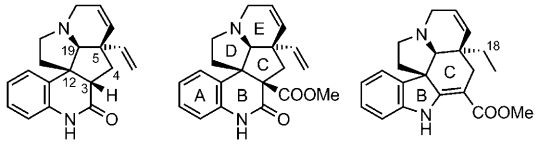

Figure 1. Structures of the *Melodinus* alkaloids (+)-meloscine [(+)-**1**], (+)-scandine [(+)-**2**], and the closely related *Aspidosperma* alkaloid (−)-tabersonine [(−)-**3**].

Biosynthetically, all 14 meloquinolines known to date are likely to be derived from the parent compound (+)-scandine [(+)-**2**], which is the rearrangement product of 18,19-didehydrotabersonine, the compound thought to represent the common origin of all the *Melodinus* alkaloids on the basis of structural and chemotaxonomical data.[2] While the discovery and structure elucidation of meloscine (**1**) and other

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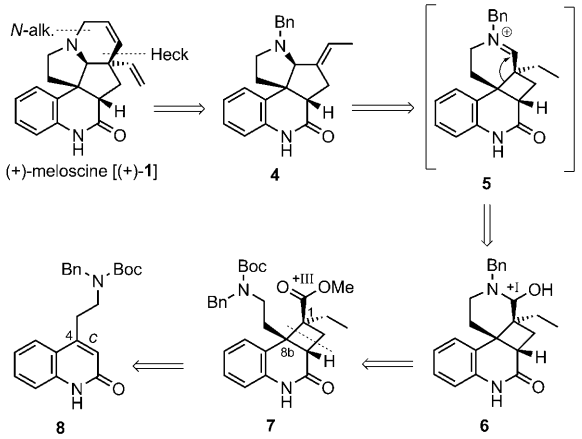
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200802383.

meloquinolines from the species *Melodinus scandens Forst.* already took place in the late 1960s,[3] no data on any kind of biological activity has been published ever since, except for the observation that certain *Melodinus* species find use in traditional chinese folk medicine as a treatment for meningitis and rheumatic heart disease.[4] In contrast to the two other main groups of B-ring expanded monoterpenoid indole alkaloids, that is, the *Cinchona* and the *Campthoteca* alkaloids, which are both well renowned for their pharmacological uses, the *Melodinus* alkaloids seem hitherto devoid of any useful biological activity, maybe due to the fact that the incorporated lactam moiety strongly impairs with the passage of melodan structures through biological membranes.

Despite the present lack of applications, *Melodinus* alkaloids are attractive targets for chemical synthesis, given both their structural uniqueness in the world of alkaloids and their complex, highly substituted central cyclopentane ring C as a challenge for synthetic organic chemistry. Two biomimetic syntheses of the melodan skeleton were reported almost simultaneously in 1984, both starting from derivatives of (−)-tabersonine [(−)-**3**] or its dihydro-derivative (−)-vincadifformine. Rearrangement of the B,C-ring system was achieved by either α-ketol rearrangement,[5] or flow thermolysis of an intermediate aziridine.[6] The latter method was also applicable to the synthesis of natural (+)-meloscine [(+)-**1**] and (+)-scandine [(+)-**2**] from 18,19-didehydrotabersonine.[7] A different entry into the melodan skeleton was described starting from the alkaloid leuconolam by an intramolecular Michael addition.[8] Besides these semisynthetic approaches to the melodan skeleton, only a few total-synthetic studies have been published to date. The only successful completion of the synthesis of racemic meloscine (**1**) was reported by Overman et al. in 1989.[9] From a synthetic point of view, the construction of the two quaternary carbon centers C5 and C12 can be considered the pivotal steps of any synthesis of the melodan skeleton.[10] In Overman's synthesis, C12 was constructed as part of the tricyclic core C,D,E by the powerful aza-Cope rearrangement, Mannich cyclization strategy, while C5 was already established at an early stage of the synthesis by a $ZnBr_2$-promoted silyl enol ether alkylation. A different approach to the core structure of racemic scandine (**2**) was reported recently by Denmark et al., which relies on an intramolecular Heck cyclization for the formation of carbon center C12.[11] However, no substituent was introduced at C5, thus the synthesis remained limited to the pentacyclic melodan core structure. Finally, a single approach to an asymmetric synthesis of *Melodinus* alkaloids has been reported, but this sequence remained limited to the tricyclic core C,D,E.[12]

In a fundamentally new approach to the synthesis of *Melodinus* alkaloids, we planned to construct the quaternary stereogenic center C12 by a [2+2]-photocycloaddition reaction to the *c*-bond of a 4-substituted 2(1*H*)quinolone representing the lower two rings A and B of meloscine (**1**). Thus, we wanted to employ both the well-known suitability of quinolones for photochemical reactions[13] as well as the inherent power of the [2+2]-photocycloaddition to build up multiply substituted carbon centers.[14] Moreover, given the possibility of the [2+2]-photocycloaddition being conducted in an enantioselective fashion,[15] this photochemical key step should also give rise to a first enantioselective total synthesis. Our complete retrosynthetic analysis of (+)-meloscine [(+)-**1**] based on these consideration is outlined in Scheme 1. As in the following discussions, the absolute configuration of all products and intermediates is initially omitted for the sake of clarity, and descriptors (+)/(−) will be introduced only at the stage of the enantioselective synthesis (see below). Accordingly, substances were initially prepared as racemates and will be discussed as such unless otherwise indicated.



Scheme 1. Retrosynthetic analysis of (+)-meloscine [(+)-**1**].

As the final step of our synthetic plan, the ring closure of the tetrahydropyridine E ring of meloscine would occur as an intramolecular Heck reaction[16] after removal of the benzyl (Bn) protective group (PG) and appropriate *N*-alkylation of the tetracyclic precursor **4** (Scheme 1). It is important to note, that after β-hydride elimination this Heck reaction would provide the vinyl side chain of meloscine in a straightforward fashion, thus rendering its separate construction by elimination[9b] unnecessary.

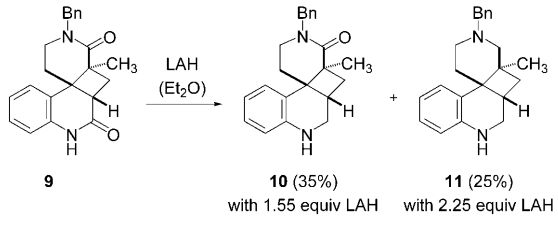
Precursor **4** was in turn envisioned to be the direct product of a Wagner–Meerwein-like 1,2-rearrangement[17] of the iminium ion **5** followed by an exocyclic elimination, which was already shown to take place selectively in earlier test systems.[18] This rearrangement would convert the [4.2.0]-bicyclic substructure incorporating the cyclobutane motif accessible from quinolone photochemistry into the [3.3.0]-bicyclic structure representing the rings C and D of meloscine in one single step. Iminium ion **5** would be derived from hemiaminal **6** by elimination of the hydroxy group, and rearrangement precursor **6** should result from reduction and ring closure of the [2+2]-photocycloaddition (PCA) product **7** of 4-aminoethylquinolone **8** and an α-ethyl acrylate. The early intermediate **7** would already provide all the atoms of the tetracyclic A,B,C,D substructure of meloscine as well as

the C_2 side chain to be converted into the final C5 vinyl substituent. Moreover, with the stereochemistry at the quaternary carbon center C8b established beforehand, all following reactions should occur in a substrate-controlled, diastereoselective fashion. It turned out that, indeed, the stereochemical course of the whole synthesis could be controlled by this single quaternary center, while the retrosynthetic plan depicted in Scheme 1 had to be altered several times as the synthesis progressed. Details of our synthetic endeavor which eventually culminated in the first enantioselective total synthesis of (+)-meloscine [(+)-**1**] are given in this full account.[19]

Results and Discussion

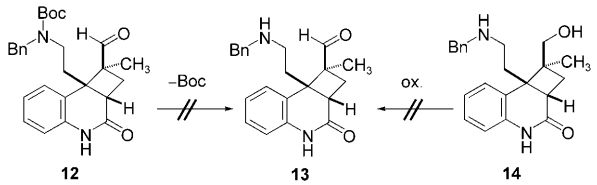
Studies towards iminium ion rearrangement: The photochemistry of protected aminoethylquinolone **8** and the synthesis of 1-alkyl substituted cyclobutanes by [2+2]-photocycloaddition reactions have already been investigated extensively.[20] Indeed, the envisioned cyclobutane **7** was readily accessible in both racemic as well as enantiomerically enriched form by the [2+2]-photocycloaddition of quinolone **8** and methyl α-ethylacrylate, although the diastereomeric ratio with respect to C1 [d.r.(*exo*/*endo*) ≈ 60:40] and the difficulties encountered in the separation of diastereoisomers somehow limited the yield of the required 1-*exo* isomer. Thus, more easily accessible 1-methyl substituted cyclobutanes were chosen as initial test substrates for the construction of rearrangement precursors, while they still retained the pivotal quaternary center at C1.

The most straightforward entry to hemiaminals or lactols such as **6** would certainly be the direct reduction of a corresponding lactam. While in most cases the reduction of *N*-alkyl lactams preferably yields the fully deoxygenated amine products, several examples have been reported resulting in lactols or the corresponding open-chain ω-aminoaldehydes.[21] Lithium aluminum hydride (LAH) reduction of lactam **9**,[20] however, only resulted in moderate yields of the two fully reduced amines **10** and **11**, and no hint of the formation of an intermediate lactol could be found (Scheme 2).



Scheme 2. Reduction of tetracyclic lactam **9** with LAH (Et_2O).

While both products **10** and **11** were of no use for our synthetic plan towards meloscine, it is interesting to note, that the lower, secondary lactam was unexpectedly more reactive towards LAH reduction than the upper, tertiary lactam. Reactions were not optimized, but in later studies AlH_3 was eventually identified as a reductive agent even more selective for the reduction of the quinolone derived anilide.[22] For the successful reductive formation of the required lactol from a lactam precursor to take place, however, the presence of an *N*-acyl protective group like the *tert*-butyloxycarbonyl (Boc) group instead of the *N*-Bn protective group as in lactam **9** seemed a necessary prerequisite.[23] Unfortunately, we were unable to perform the necessary protective group interconversions, because lactam **9** was either unreactive towards most *N*-Bn deprotection methods,[24] or showed a reductive fragmentation of the cyclobutane ring[25] under dissolved metal conditions.[26] As the desired reduction turned out to be impossible with the tetracyclic lactam **9**, we investigated the possibility of establishing the correct oxidation state (+I) of the rearrangement precursor *before* the ring closure to the [4.2.0]-bicyclic system (Scheme 3).

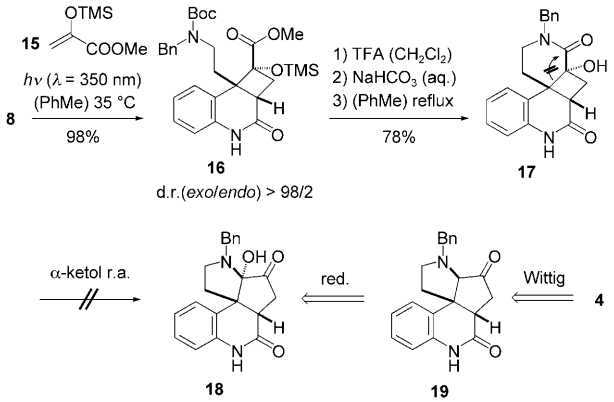


Scheme 3. Failed approaches to access the open-chain ω-aminoaldehyde **13**.

To our surprise, the up-to-now straightforward *N*-Boc deprotection of cyclobutane photocycloaddition products [10 vol% trifluoroacetic acid (TFA) in CH_2Cl_2] failed in the case of aldehyde **12**,[20] and resulted exclusively in the fragmentation of the cyclobutane unit.[25] Less acidic conditions or milder deprotection agents, for example, $ZnBr_2$[27] or TMS-I[28] did not give any conversion. As an access to aminoaldehyde **13** or its ring-closed hemiaminal form remained impossible also by the attempted reduction of free *N*-Boc deprotected aminoesters, the oxidation (ox.) of free aminoalcohol **14** was investigated as a final possibility. While it was eventually possible to gain access to an *O*-ethylated hemiaminal derivative by oxidation of **14** with *o*-iodoxybenzoic acid (IBX) in DMSO, this transformation turned out to be hardly reproducible and the product suffered from both low yields and purity. Moreover, the obtained *N*,*O*-acetal showed no tendency towards the planned formation of a *N*-Bn iminium ion such as **5**, and no trace of any rearranged product could be detected either.[25] Given the overall discouraging results obtained in our approaches to α-alkyl substituted rearrangement precursors, the inaccessibility of *N*-acyl substituted precursor structures and the seemingly very low tendency of *N*-alkyl iminium ions towards rearrangement, we finally abandoned our original synthetic plan. The possibility of an oxidation[29] of tetracyclic piperidines, which were also accessible by means of a [2+2]-photocycloaddition,[30] was left uninvestigated. Instead, we turned our focus from α-alkyl to α-hydroxy substituted lactams giving rise to

the envisioned 1,2-rearrangement as an α-ketol rather than a Wagner–Meerwein-type rearrangement.

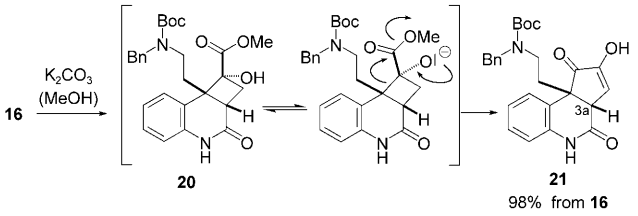
Studies towards α-ketol rearrangement: The construction of a tetracyclic lactam bearing a hydroxy instead of an alkyl substituent at the α-position required the [2+2]-photocycloaddition of an α-oxy substituted acrylic acid derivative. As there was no precedence of any such [2+2]-photocycloaddition, it came as a pleasant surprise that enol ether **15**[31] derived from methyl pyruvate proved to be an excellent substrate for the planned transformation.[32] Irradiation of a toluene solution of quinolone **8** and an excess of enol ether **15** with UV light ($\lambda = 350$ nm) gave the desired *cis*-fused cyclobutane **16** as a single diastereoisomer in almost quantitative yield. Obviously, the α-silyloxy substituent of acrylate **15** and the resulting captodative electronic situation at C-α exhibit a favorable effect on the course of the [2+2]-photocycloaddition, as both yield and stereoselectivity surpassed the values obtained with any α-alkyl substituted acrylate investigated earlier.[20] Using established conditions, cyclobutane **16** was readily converted into the α-hydroxy lactam **17** by *N*-Boc deprotection and thermal cyclization of the free aminoester in refluxing toluene. Thermal conditions simultaneously affected the cleavage of the *O*-TMS (trimethylsilyl) protective group (Scheme 4).



Scheme 4. Synthesis of α-hydroxylactam **17** and the failed plan to access intermediate **4** with an α-ketol rearrangement.

With lactam **17** in hand, we tried to carry out the skeletal rearrangement to hemiaminal **18** under both base and acid catalyzed conditions. Reduction of **18** to its corresponding amine **19** and introduction of the C_2 side chain by carbonyl olefination should then give access to intermediate **4** (Scheme 1). However, the rearranged product **18** remained unaccessible as lactam **17** showed no conversion under all conditions investigated. It seems reasonable to assume, that the enthalpic gain from the relief of ring strain plus the formation of one carbonyl group is by far insufficient to make up for the energetic loss connected with the sacrifice of the six-membered lactam ring. Although it was possible to convert cyclobutane **16** into an aminoalcohol, representing a diol derivative of **14**, attempts to realize an α-hydroxy assisted iminium ion rearrangement were not undertaken. Instead, a different kind of rearrangement was discovered in the fully protected cyclobutane **16**.

***Retro*-benzilic acid rearrangement and reductive amination**: The rearrangement was discovered when the basic conditions previously applied to lactam **17** were used for the reaction of cyclobutane **16** itself. To our amazement, the yet impossible ring expansion from a cyclobutane to a cyclopentane was readily realized by simply stirring **16** in methanolic K_2CO_3 for several hours at room temperature. After *O*-TMS cleavage was accomplished within a few minutes, the free α-hydroxy ester **20** smoothly underwent a *retro*-benzilic acid like rearrangement[33] to give a cyclopentane-1,2-diketone which exclusively existed in its tautomeric enol form **21** (Scheme 5).



Scheme 5. *Retro*-benzilic acid rearrangement of cyclobutane **16**.

While no attempts were made to isolate the free alcohol **20**, its formation and thus the stepwise course of the reaction was clearly evident from TLC and NMR analysis of the reaction mixture. Ketone **21** could be isolated as a single product in excellent yield and purity after simple hydrolytic work-up of the reaction mixture. The fact, that the *retro*-benzilic acid rearrangement of cyclobutane **20** took place under very mild conditions in excellent yields, while the initially sought-after rearrangement of any closed [4.2.0]-bicyclic system had been impossible even under drastic conditions is maybe best explained by stereoelectronic arguments. Thus, the imine position in closed [4.2.0]-bicycles such as **5** or **17** is sterically fixed in a presumably unreactive position, in which the migration of the tertiary benzylic center would have to occur into the node-plane of the imine π* orbital.[17] In contrast, cyclobutane **20** can access reactive conformations with the ester carbonyl group being positioned vertically to the migrating bond by free rotation, thus enabling perfect overlap of the migrating σ-bond and the ester π* orbital, the target of migration (Figure 2). Regardless of any enthalpic or entropic considerations, this observation convinced us to abandon any further attempts of iminium ion or α-ketol rearrangements.

Enone **21** was configurationally stable under basic conditions although the high acidity of bridgehead proton H3a would render epimerization theoretically possible. This was evident from ^{1}H NMR analysis of **21** in a CD_3OD solution, which indicated a quick H,D-interchange at C3a but no al-

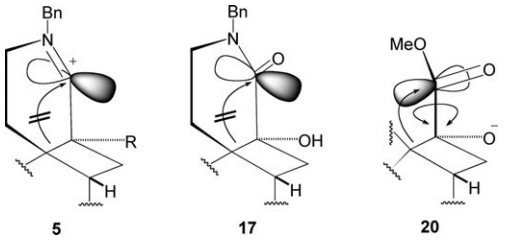
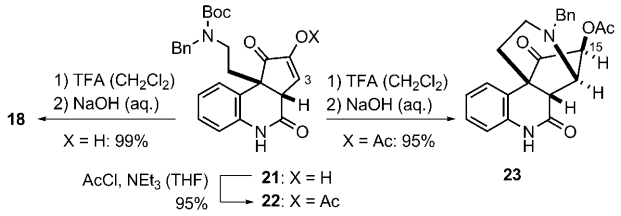


Figure 2. Stereochemical conditions in the rearrangement precursors **5**, **17**, and **20**.

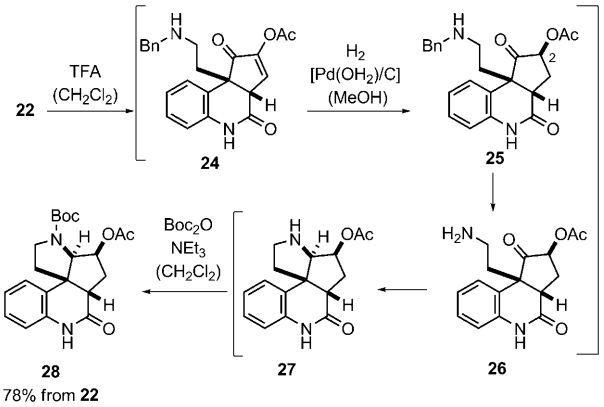
teration of any other proton signal. The established *cis* annelation of rings B and C was kept intact by the quaternary benzylic center even though the adjacent position C3a was strongly prone to deprotonation. Following *N*-Boc deprotection and basic work-up, the free aminoketone derived from **21** instantaneously cyclized to give the hemiaminal **18** in



Scheme 6. Further conversions of rearrangement product **21**.

quantitative yield (Scheme 6). Using this preparatively simple three-step sequence of [2+2]-photocycloaddition, *retro*-benzilic acid rearrangement, and deprotection/ring closure we were able to access the tetracyclic product **18** in 95% overall yield on a multi-gram scale with no chromatographic purification step being necessary. Following this first breakthrough, extensive efforts were made to further convert hemiaminal **18** into its corresponding deoxygenated amine **19** (Scheme 4). However, none of the applied reductive conditions, for example, by employing $Na(CN)BH_3$, $Na(OAc)_3BH$, Et_3SiH/TFA, TMS-I[34] or heterogeneous conditions with Pd or Pt catalysts, gave a defined product. If any conversion of starting material was detectable at all, it had generally resulted in a rapid decomposition giving a complex mixture unsuitable even for rough, preliminary analysis. Attempts to achieve carbonyl olefination prior to reduction were equally unsuccessful, as were any attempts of reduction or olefination with the *N*-Boc protected open-chain precursor **21**. In summary, the immediate rearrangement products **21** and **18** turned out to be dead ends, probably due to the presence of the latent 1,2-dione moiety. Although hemiaminal **18** was one single, stable compound in NMR measurements, it seems likely that open-chain and/or tautomeric aminoketone forms played a decisive role under reductive conditions. This was underlined by the observation, that the $NaBH_4$ reduction of hemiaminal **18** only resulted in the formation of open-chain cyclopentane-1,2-diols, clearly being the product of an opened 1,2-dione form of **18**. In order to overcome the problems associated with the 1,2-dione structure, rearrangement product **21** was chemically fixed in its enol form by acetylation. Indeed, the obtained enol acetate **22** showed a profoundly different reactivity as compared to the free enol **21** after *N*-Boc deprotection and basic work-up. No 1,2-addition to the carbonyl group could by detected at all, instead, the free amine rapidly underwent a 1,4-addition to the β-position at C3, resulting in the [3.2.1]-bicyclic substructure of product **23** (Scheme 6).

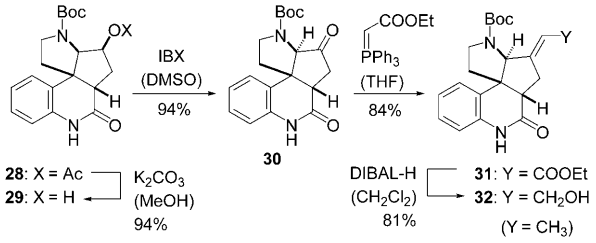
Interestingly, piperidine **23** was obtained as a single diastereoisomer with the shown *exo*-configuration at C15. Attempted purification by silica gel chromatography led to widespread decomposition as **23** was unstable under acidic conditions. Accordingly, the formation of **23** was completely suppressed as long as the nucleophilic amine was kept protonated, that is, no basic work-up of the *N*-Boc deprotection mixture was undertaken. When this acidic mixture was subjected directly to reductive amination conditions using hydrogen gas and Pearlman's catalyst [$Pd(OH)_2$/C] in MeOH, a clean reaction took place, and after renewed *N*-Boc protection of the crude product mixture a single pyrrolidine product **28** could be isolated in 78% yield over a total of five synthetic transformations (Scheme 7).



Scheme 7. Formation of pyrrolidine **28** under hydrogenation conditions. (Only the free amines are shown for the sake of clarity.)

The course of the reaction as it is shown in Scheme 7 was elucidated by means of ^{1}H NMR analysis of the reaction mixture. Thus, benzylamine **24** was first hydrogenated at its enol double bond to give cyclopentanone **25** in a diastereoselective fashion. This hydrogenation proceeded very quickly and was basically finished after less than 10 minutes. The diastereoselectivity of this hydrogenation showed a remarkable strong dependence on the reaction temperature. While at <15 °C **25**, and thus the final product **28**, was formed as the C2 *exo*-isomer exclusively, temperatures of >25 °C led to the formation of a 50:50 mixture of C2 diastereoisomers. Thus, the reaction mixture was best cooled with an ice-bath before initiating the reductive sequence. Subsequent *N*-de-

benzylation to the free primary amine **26** probably represents the rate-limiting step of the overall sequence and required reaction times of more than 12 h. Attempts to speed up the debenzylation step by heating to 50 °C quickly led to widespread decomposition. Intramolecular reductive amination giving the free pyrrolidine **27** concluded the reductive sequence. *N*-Boc protection to **28** finally allowed for an easy chromatographic purification of the product. The sequence outlined in Scheme 7 was conveniently performed as a one-pot procedure by simply diluting the TFA-acidic mixture of **24** with MeOH, adding the catalyst and stirring under a H_2 atmosphere over night. With **28** in hand, we finally had access to an intermediate displaying both the [3.3.0]-bicyclic substructure and the correct oxidation state at the nitrogen-adjacent carbon center. What was left to do, was the addition of the missing C_2 unit by a carbonyl olefination. Thus, acetate **28** was readily saponified to its free alcohol **29** and oxidized to give ketone **30** (Scheme 8). At this stage, the relative *exo*-configuration of the hydroxy group at C2 was crucial, as the diastereomeric alcohol failed to yield the desired ketone and decomposed into a complex, dark-red mixture. *N*-Boc protected ketone **30** could not be converted into its free amine or any other *N*-alkylated products due to the high intramolecular nucleophilicity of the pyrrolidine nitrogen, which led to the formation of an unstable aziridine-aminal. However, carbonyl olefination using the stabilized reagent $Ph_3P{=}CHCOOEt$ in refluxing THF went very smoothly, giving the α,β-unsaturated ester **31** as a single diastereoisomer, which could be converted into the allylic alcohol **32** with DIBAL-H in CH_2Cl_2 at −45 °C.



Scheme 8. Formation and carbonyl olefination of *N*-Boc protected ketone **30**.

In sharp contrast to the Wittig reaction giving ester **31**, any attempts to achieve a carbonyl olefination resulting in a plain alkyl, for example, a methyl substituent remained fruitless. Simple Wittig salts or phosphonic acid esters did not lead to any conversion of ketone **30**, presumably due to a competing deprotonation of the adjacent methine proton and the formation of an unreactive enolate. Less acidic reagents like cyclic phosphonamides[35] or a dimetallic chromium-samarium reagent[36] were also ineffective. In the end, we decided to rely on α,β-unsaturated ester **31** and allylic alcohol **32** as precursors for the final ring closure although this implied sacrificing the Heck-promoted formation of the vinyl side-chain of meloscine as planned earlier (Scheme 1).

Studies towards intramolecular ring closure: *N*-Boc deprotection of **31**/**32** and subsequent *N*-alkylation allowed for the straightforward synthesis of a number of precursors **33**–**36** for the final intramolecular ring closure in good yields (Figure 3).

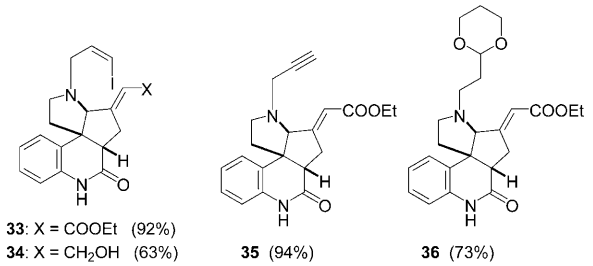
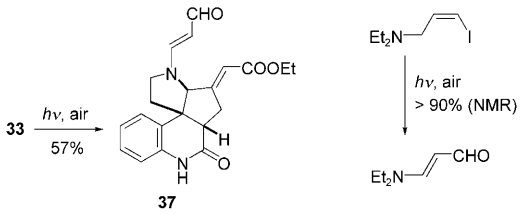


Figure 3. Precursors **33**–**36** for an intramolecular ring closure.

Especially the *Z*-iodopropenes **33**/**34**, which were available from literature-known (*Z*)-3-bromo-1-iodopropene[37] and which already incorporated the desired double-bond configuration of the melodan skeleton, were investigated intensively under a variety of cyclization conditions. A promising option seemed to be the metalation of **33** with subsequent Michael addition of the alkenyl metal species to the α,β-unsaturated ester moiety. Much to our surprise, however, ester **33** was basically inert to many metalating agents like Mg or Li metal, *i*PrMgBr, MeLi, *n*BuLi or even *t*BuLi. In fact, the iodovinyl group of substrate **33** remained completely untouched upon the addition of up to three equivalents of *t*BuLi at room temperature and even greater excesses of reagent or heating only led to an unspecific decomposition. It seems that due to the poor reactivity of the vinyl iodide, basic organometallic reagents led to an efficient, multiple deprotonation of the substrate rather than giving the desired halogen-metal exchange. Only under very drastic conditions (>5 equiv *t*BuLi at room temperature) some traces of proto-deiodination product could be observed. Large excesses of SmI_2 (THF)[38] resulted in the reduction of the α,β-unsaturated ester double bond, but again the vinyl iodide remained intact. Consequently, any attempted transmetallation reactions to form a soft nucleophile suitable for addition to the α,β-unsaturated ester remained futile.[39] Attempted radical cyclizations of **33**/**34** were equally unsuccessful[40] and exclusively resulted in unspecific decomposition. Finally, the attempted Heck-type ring closure[41] of **33**/**34** failed as either no oxidative addition of Pd could be realized, or a rapid *N*-deallylation occurred if more drastic conditions ($T > 100$ °C) were applied. The same problem was encountered in preliminary studies concerning an ene-yne-cyclization of propargylamine **35** with Au, Ag or Pt salts. Finally, acetal **36** was planned to serve as a precursor for a SmI_2 induced carbonyl radical cyclization,[42] yet this approach failed due to the extreme instability of the intermediate free β-aminoaldehyde.[43] In summary, no intramolecular ring closure could by realized under any conditions in any of the precursors **33**–**36**. However, an unusual photo-

chemical oxidation was discovered when the radical-cyclization of **33** was attempted under UV irradiation (Scheme 9).



Scheme 9. Photochemical oxidation of (*Z*)-3-iodoallylamines to β-aminoacroleines.

The formation of β-aminoacroleine **37** was in fact most efficient when using air as an oxidant, sunlight as the UV source and NEt_3 as a scavenger for liberated iodide, thus representing a nice example of green photochemistry.[44] The reaction was also applicable to simpler iodoallylamines as shown for the diethylamine analogue (Scheme 9). However, the synthetic value of this newly found photooxidation remains limited, as the β-aminoacroleine products are also available from the simple 1,4-addition of amines to propiolaldehyde. In spite of its continuous failure in all ring-closing attempts, ester **33** still proved to be valuable, as it spontaneously crystallized from a $CDCl_3$ solution to form big, off-white plates suitable for single crystal X-ray structure analysis (Figure 4, see also Experimental Section and Supporting Information).

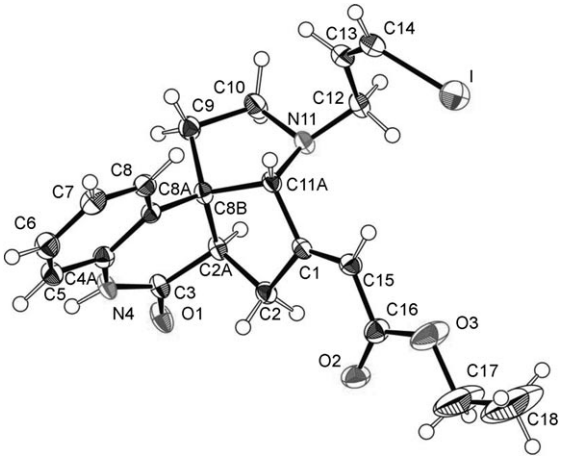
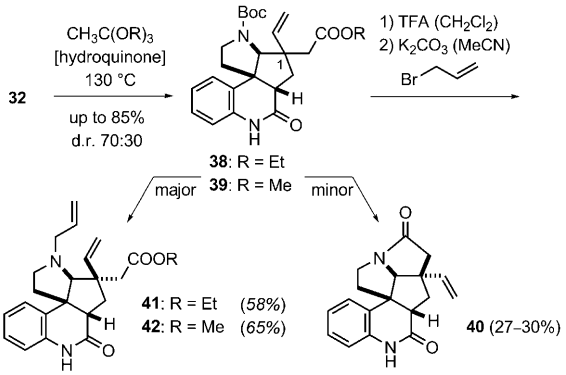


Figure 4. Structure of compound **33** in the crystal.

This obtained structure served as an unambiguous proof for the stereochemical assignments made previously on the basis of ^{1}H NOE measurements, but it also indicated an unfavorable steric proximity of the vinyl moiety and the acidic proton at C11a.

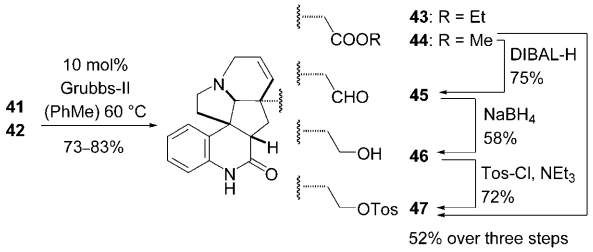
Claisen rearrangement and ring-closing metathesis: Due to the continuous failure of the attempted intramolecular closure of the final tetrahydropyridine E ring of meloscine, we decided to decouple the two synthetic steps of ring closure and formation of the quaternary carbon center and to build up the final ring of meloscine by a combination of Claisen rearrangement[45] and ring-closing metathesis.[46] Indeed, the final quaternary carbon center could be established without problems by performing a thermal Johnson–Claisen rearrangement[47] on the *N*-Boc protected allylic alcohol **32**. Using triethylorthoacetate or trimethylorthoacetate with hydroquinone as acidic catalyst, alcohol **32** could be converted into the corresponding rearrangement products **38**/**39**, both of which were formed as mixtures in almost identical diastereomeric ratios of d.r. ≈ 70:30 (Scheme 10).



Scheme 10. Claisen rearrangement of **32** and *N*-allylation of the product mixture.

Separation of the diastereoisomeric mixtures was conveniently achieved after the subsequent step of *N*-Boc deprotection and *N*-allylation during which the minor isomer quantitatively cyclized to give the pentacyclic lactam **40** (>90% rel. to d.r.). Allylamines **41** and **42** were obtained in 58 and 65% yield, respectively, and were thus clearly derived from the major diastereoisomers. The configuration assignment of the obtained products was initially based on ^{1}H NOE measurements, and was confirmed later on in the course of the synthesis (Scheme 11). In order to obtain satisfactory yields in the rearrangement step, however, some optimization work turned out to be necessary, as standard conditions, that is, refluxing in 7–10 equivalents of $CH_3C(OEt)_3$ at 145°C, only provided mediocre yields of 30–40% of product **38**. Moreover, no full conversion of the starting alcohol could be achieved even under prolonged heating and with excessive amounts of acid catalysts, and the reaction mixture always contained significant amounts (20–30%) of the substrate acetate arising from hydrolysis of the intermediate orthoester. Yields were slightly better when using $CH_3C(OMe)_3$, but still no more than 45% of **39** could be isolated even when a complete conversion of the substrate was forced by further heating to 150°C. Microwave assisted thermolysis[48] and other catalytic methods[49] to overcome these

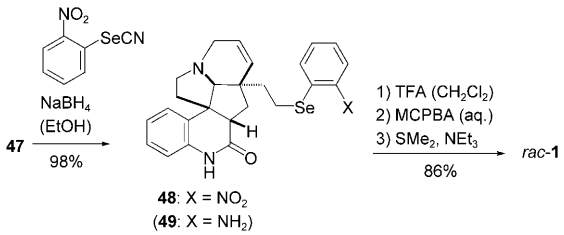
common problems of the Johnson–Claisen rearrangement seemed quite incompatible with the *N*-Boc pyrrolidine structure of the substrate. High yields could eventually be realized when the reaction mixture was concentrated into a thick gum with $c(\mathbf{32}) \approx 2$–$3\ \mathrm{mol\,L^{-1}}$ after the initial formation of a homogeneous mixture. Using these high concentration conditions a total of 85% of **39** was obtained after only a few hours while keeping the temperature below 135°C. The diastereomeric ratio (d.r. ≈ 70:30) with respect to C1 remained completely unchanged under all conditions, and no difference was observed when using the different orthoacetate reagents either. Thus, no attempts were made to improve the diastereomeric ratio by variation of the orthoester substituent.[50] Fortunately, the required configuration at C1 was realized in the major diastereoisomer, and satisfactory yields of **41**/**42** could be obtained. Ring closing metathesis went smoothly for both allylamines **41**/**42** using Grubbs′ 2nd generation catalyst[51] in toluene and provided the ester **43**/**44**, establishing the complete pentacyclic carbon skeleton of meloscine (Scheme 11). From this point onwards, only the methyl carboxylate **44** was used for further transformations.



Scheme 11. Construction of the melodan skeleton by ring-closing metathesis and further conversions of the ester side-chain.

What remained to be done was the conversion of the ester group of **44** into the vinyl moiety of meloscine (**1**). Reduction with DIBAL-H in CH_2Cl_2 gave aldehyde **45** in good yields and subsequent $NaBH_4$ reduction provided the known alcohol **46** already used by Overman et al.[9] Purification of **46** was somehow problematic, however, due to its very high polarity and unfavorable chromatographic behavior on silica gel. Thus, purification of intermediates **45** and **46** was best omitted and the crude product was directly converted into tosylate **47** well suitable for chromatographic purification. Several attempts were made to achieve a direct elimination of the tosylate,[52] but no conversion could be achieved.

The good availability of aldehyde **45** led us to investigate a possible reduction via its enol triflate.[53] While the latter could indeed be synthesized as a mixture of *E* and *Z* isomers, no subsequent oxidative addition of Pd could be realized, and we finally had to fall back to the selenium oxide elimination[54] already established in Overman's synthesis. Tosylate **47** was thus converted to the *o*-nitrophenylselenide **48** by treatment with an excess (20 equiv) of *o*-nitrophenyl selenide anion obtained from *o*-nitrophenyl selenocyanate and $NaBH_4$ in EtOH. This reaction required long reaction times, high concentrations and the repeated addition of selenide anion solution in order to achieve full conversion. Oxidation of selenide **48** with *meta*-chloroperbenzoic acid (MCPBA) at −78°C and thermal decomposition of the selenium oxide finally gave the desired product meloscine (**1**) in 86% yield, provided that the basic nitrogen atom had been protonated previously by a slight excess of TFA (Scheme 12).



Scheme 12. Completion of the synthesis of racemic meloscine (**1**).

Spectroscopic data of racemic meloscine (**1**) (m.p. 216–220°C)[9a] were in all aspects identical to the enantiopure natural product data.[3,5,55] Interestingly, when the sequence depicted in Scheme 12 was conducted according to literature precedence[9b] without the prior addition of TFA, yields of isolated meloscine (**1**) never exceeded 20–30%. Using one equivalent of MCPBA, only very little conversion of the selenide was achieved, and more than two equivalents of MCPBA lead to widespread decomposition of the product. Amazingly, occasionally present residual contaminants of tosylate **47** could always be recovered quantitatively. Thus, the observed decomposition does not seem to result from an oxidation of the basic nitrogen atom, but rather from its reaction with the intermediate selenium oxide. Also, the quality of $NaBH_4$ was of utmost importance. When aged, partially hydrolyzed $NaBH_4$ was employed, reduction of the aromatic nitro group giving aniline **49** was a significant side reaction. Another difficulty arose from the formation of very stable aminoborane adducts at the bridgehead nitrogen atom, a problem which had already been encountered in the $NaBH_4$ reduction to alcohol **46** (Scheme 11). The exact nature of the $NaBH_4$ contaminants leading to aminoborane formation remained unclear, but the identical adducts were obtained by the treatment of pentacyclic melodan products with BH_3·THF, as was shown for ester **44** (Figure 5). Both side reactions could be completely suppressed, however, when using fresh $NaBH_4$ under anhydrous conditions. Starting from quinolone **8**, racemic meloscine (**1**) was thus available in 15 linear steps and 9% overall yield. Moreover, the newly established synthesis exclusively consists of experimentally simple, robust and reliably reproducible reactions. With the exception of $NaBH_4$ and DIBAL-H reductions, anhydrous conditions were not necessary and none of the reagents or intermediates needed to be freshly prepared. In a single experiment, alcohol **46** was converted into the hexacyclic ether **50** by oxymercuration with $Hg(OOCCF_3)_2$ and reductive workup with $NaBH_4$ according to Overman's syn-

thesis of deoxoapodine (**51**)[9b] (Figure 5). However, yields were low (<15%) and **50** could only be isolated as a crude product with about 80% purity according to NMR analysis.

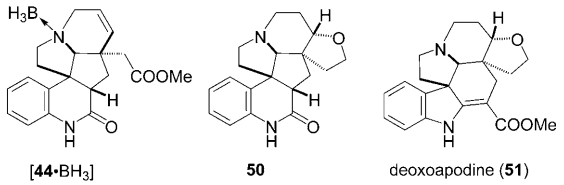
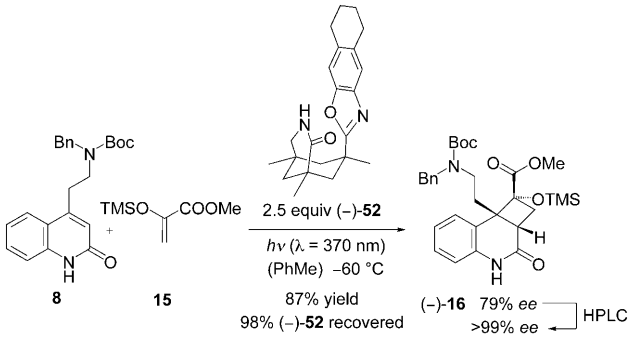


Figure 5. Aminoborane adduct of ester **44** and compound **50** closely resembling the aspidosperma alkaloid deoxoapodine (**51**).

Enantioselective total synthesis of (+)-meloscine [(+)-1]: For the established synthesis of racemic meloscine (**1**) to be conducted in an enantioselective fashion, the initial key step of the [2+2]-photocycloaddition was performed in the presence of the chiral complexing agent (−)-**52**.[56] Using low-temperature conditions and an irradiation wavelength of $\lambda =$ 370 nm (Rayonet RPR-3500 Å lamps), the photocycloaddition product (−)-**16** was obtained with an enantiomeric excess (*ee*) of 79% *ee* in 87% yield (Scheme 13).



Scheme 13. Photochemical key step of the enantioselective total synthesis.

The obtained degree of enantioselectivity was in good accordance with the results found earlier in enantioselective [2+2]-photocycloaddition reactions of quinolone **8** and α-alkyl substituted acrylates.[20] Also, the enantiomeric excess was completely unaffected by variations in substrate concentrations. Considering that only 5.0 mol% of complexing agent (−)-**52** were actually lost in this photocycloaddition reaction, the reaction may reasonably be considered as "quasi-catalytic" with respect to (−)-**52**. In contrast to the corresponding racemic reaction (Scheme 4), a slightly longer irradiation wavelength was necessary to achieve these high recovery rates of the complexing agent (−)-**52**. With $\lambda =$ 350 nm (LZC-UVA lamps) only 60–70% of (−)-**52** could be re-isolated, although the complexing agent shows no significant UV absorption at $\lambda > 320$ nm. Unfortunately, the required longer irradiation wavelength somehow limited the amount of obtainable photoproduct, as due to the overall smaller spectral overlap only low concentration solutions of quinolone **8** ($c =$ 5–10 mM) could be converted within a reasonable amount of time. Long irradiation times of more than 10 h necessary for highly concentrated substrate solutions or large volume irradiation vessels resulted in the formation of by-products and a drop of yield to 70–75% of (−)-**16**. The enantiomeric excess of (−)-**16** could be further improved by either recrystallization of the racemate from *n*-hexane or by semipreparative HPLC separation (ChiralPak AD). While racemate recrystallization involved the sacrifice of 10% of the desired enantiomer, HPLC separation of the enantiomers was basically quantitative, thus giving a total of 76% of enantiomerically pure product (−)-**16** (>99% *ee*, HPLC). With (−)-**16** in hand, the previously established sequence of rearrangement (Scheme 5), reductive amination (Scheme 7), Wittig reaction (Scheme 8), Claisen rearrangement (Scheme 10), ring-closing metathesis (Scheme 11) and construction of the vinyl group (Scheme 11,12) could be performed without any experimental changes. No trace of racemization was observed at any step (chiral HPLC, see Supporting Information), and all transformations gave yields very close to those obtained in the racemic reactions, despite some slight differences in the extraction and chromatographic behaviors. Finally, the enantiomerically pure (+)-meloscine [(+)-**1**] (m.p. 172–176 °C) obtained from (−)-**16** well matched with the natural product with regard to both optical rotation and melting point.[3a,b] The latter is significantly lower than for the racemic product probably due to sterically impaired intermolecular hydrogen bonding.

Conclusion

In summary, we have developed a new and efficient synthesis of the unusual monoterpenoid indole alkaloid meloscine (**1**) in 15 steps and 7–9% overall yield. Although our original, very short synthetic plan could not be realized and several additional, partially unprecedented reactions had to be included, the newly established sequence gives for the first time smooth access to the pentacyclic melodan carbon skeleton on a gram-scale. We especially want to emphasize the experimental simplicity and robustness of the individual steps. The established reaction sequence was easily scaled up without any experimental changes to give 1.4 grams of intermediate **44** in a single run starting from quinolone **8** without further optimization. Using the chiral complexing agent (−)-**52** already used for a variety of enantioselective transformations in our group,[15,20,57] the synthesis could also be conducted in an enantioselective fashion, thus being the first natural product synthesis employing an enantioselective [2+2]-photocycloaddition as its key step.[58] In addition, the newly found combination of [2+2]-photocycloaddition and *retro*-benzilic acid rearrangement may serve as an attractive new possibility for the construction of annelated cyclopenta-1,2-diones and as a starting point for various further reactions also described in this paper.

Experimental Section

General: All commercially available chemicals were used as received without further purification. Reactions involving the water-sensitive chemicals DIBAL-H or $NaBH_4$ were performed in dried glassware under argon using anhydrous solvents. Photochemical transformation were performed in Duran-glass tubes ($d=1.0$ cm) in a merry-go-round apparatus using 16 fluorescent lamps LZC-UVA ($\lambda=350$ nm) or RPR-3500 Å ($\lambda=370$ nm) at 35 °C. TLC: Merck glass sheets (0.25 mm silica gel 60, F254), eluent given in brackets; detection by UV. Flash chromatography was performed on silica gel 60 (Merck, 230–400 mesh) (dimensions of columns given as [diameter]×[height]) with the indicated eluent. Common solvents for chromatography [pentane (P), EtOAc, CH_2Cl_2, MeOH] were distilled prior to use. ^1H and ^{13}C NMR spectra were recorded in the indicated solvent at ambient temperature unless otherwise indicated. Chemical shifts are reported relative to solvent residue signals as internal standard. Apparent multiplets, which occur as a result of the accidental equality of coupling constants of magnetically non-equivalent protons are marked as virtual (virt.). The multiplicities of the ^{13}C NMR signals were determined by DEPT experiments. Signals in the ^{13}C NMR spectra which may be interchanged are marked with an asterisk (*). The preparation and analytical data of compounds **10**, **11**, **14**, **34**–**38**, **41**, **43**, **49**, **50** and the aminoborane adduct of compound **44** are reported in the Supporting Information. ^{13}C NMR spectra of all new compounds, chiral HPLC data of (−)-**16** and selected intermediates, full spectroscopic data of (+)-meloscine [(+)-**1**] and emission spectra of the fluorescent lamps used in this work are also presented in the Supporting Information.

(−)-(1*R*,2a*S*,8b*R*)-8b-{2-[Benzyl(*tert*-butoxycarbonyl)amino]ethyl}-3-oxo-1-[(trimethylsilyl)oxy]-1,2,2a,3,4,8b-hexahydrocyclobuta[*c*]quinoline-1-methyl carboxylate (16)

Racemic [2+2]-photocycloaddition: A solution of quinolone **8** (6.81 g, 18.0 mmol) and enol ether **15** (17.0 mL, 15.1 g, 90.0 mmol, 5 equiv) in toluene (582 mL) was irradiated with LZC-UVA lamps ($\lambda=350$ nm) at 35 °C in three batches (200 mL each) for 3.0 h. After evaporation of the solvent, the residue was recrystallized from petroleum ether (80–110 °C) to give the desired product as an off-white crystalline solid. The remaining mother liquid was concentrated and subjected to flash chromatography (5.0×30 cm, P/EtOAc 4:1→1:1) to give some additional product as a white foam. In total, cyclobutane **16** (9.72 g, 17.6 mmol, 98 %) could be isolated in nearly quantitative yield. $R_f=0.78$ (EtOAc, [UV]); m.p. 128–130 °C; ^1H NMR (500 MHz, [D$_6$]DMSO, 80 °C): $\delta=9.77$ (br, 1H, NH), 7.29–7.20 (m, 3H, H_{Bn}), 7.16 (virt. t, $^3J=8.1$ Hz, 1H, H_6), 7.05 (d, $^3J=7.1$ Hz, 2H, H_{Bn}), 7.02 (d, $^3J=7.6$ Hz, 1H, H_8), 6.96 (virt. t, $^3J=7.3$ Hz, 1H, H_7), 6.87 (d, $^3J=7.9$ Hz, 1H, H_5), 4.23 (d, $^2J=15.4$ Hz, 1H, CH*H*Ph), 4.17 (d, $^2J=15.4$ Hz, 1H, C*H*HPh), 3.73 (s, 3H, OCH_3), 2.97 (dd, $^2J=11.3$, $^3J=9.3$ Hz, 1H, CHH_{exo}), 2.91 (ddd, $^2J=13.8$, $^3J=11.9$, $^3J=4.3$ Hz, 1H, CH*H*N), 2.79 (dd, $^3J=9.3$, $^3J=9.2$ Hz, 1H, $C_{2a}H$), 2.53 (ddd, $^2J=13.8$, $^3J=11.0$, $^3J=4.7$ Hz, 1H, C*H*HN), 2.02 (dd, $^2J=11.3$, $^3J=9.2$ Hz, 1H, CH_{endo}H), 1.90 (ddd, $^2J=12.1$, $^3J=11.9$, $^3J=4.7$ Hz, 1H, RCH*H*), 1.60 (ddd, $^2J=12.1$, $^3J=11.0$, $^3J=4.3$ Hz, 1H, RC*H*H), 1.38 [s, 9H, OC(CH_3)$_3$], −0.16 ppm [s, 9H, Si(CH_3)$_3$]; ^{13}C NMR (90 MHz, $CDCl_3$): $\delta=$ 173.1 (s, COOMe), 170.3 (s, CONH), 155.5 (s, CO_{Boc}), 138.1 (s, C_{ar}), 136.9 (s, C_{ar}), 131.2 (d, C_8H), 128.4 (d, C_{ar}H), 128.2 (d, C_{ar}H), 127.9 (d, C_{ar}H), 127.2 (d, C_{ar}H), 122.7 (d, C_7H), 119.5 (s, C_{ar}), 115.7 (d, C_5H), 80.2 (s, C_1), 79.8 [s, *C*(CH$_3$)$_3$], 53.4 (s, C_{8b}), 52.1 (q, O*C*H$_3$), 50.4 (t, CH_2Ph), 42.5 (t, CH_2N), 37.3 (t, *C*HH), 36.9 (t, RCH_2), 36.8 (d, CO*C*H), 28.3 [q, C(*C*H$_3$)$_3$], 0.7 ppm [q, Si(CH$_3$)$_3$]; IR (KBr): $\tilde{\nu}=3212$ (w, br, CONH), 3065 (w, C_{ar}H), 2975 (m, C_{al}H), 1720 (s, COOMe), 1692 (vs, CON), 1594 (s), 1251 (m), 1172 (m), 843 (m), 754 (m), 700 cm^{-1} (m); MS (70 eV): *m*/*z* (%): 552 (1) [M^+], 378 (31), 322 (18), 220 (46) [BocNBnCH$_2^+$], 159 (100) [RCH$_3^+$], 120 (80) [BnNCH$_2^+$], 91 (38) [C$_7$H$_7^+$], 57 (54) [*t*Bu$^+$]; HRMS (70 eV): *m*/*z*: calcd for $C_{30}H_{40}N_2O_6Si$: 552.2656 [M^+], found 552.2658; elemental analysis calcd (%) for $C_{30}H_{40}N_2O_6Si$: C 65.19, H 7.29; found: C 65.05, H 7.34.

Enantioselective [2+2]-photocycloaddition: According to the above procedure, but with the addition of 2.5 equiv of the chiral complexing agent (−)-**52** (186 mg, 528 μmol, 2.5 equiv) and conducting the irradiation with RPR-3500 Å lamps ($\lambda=370$ nm) at −60 °C, cyclobutane (−)-**16** (101 mg, 183 μmol, 87 %) was isolated with 79 % *ee*. 98 % of the complexing agent were recovered after the reaction. The enantiomeric excess of (−)-**16** could be further improved by either recrystallization of the racemate from *n*-hexane or by semipreparative HPLC (Chiralpak AD, 250×20 mm I.D., 10 μm, *n*-hexane/*i*PrOH 90:10, 19 mL min^{-1}). Using the latter method, enantiopure cyclobutane (−)-**16** (>99 % *ee*) was obtained as a white foam in 76 % overall yield. $[\alpha]_D^{20}=-14.7$ ($c=1.0$ in CH_2Cl_2); chiral HPLC (Chiralpak AD, *n*-hexane/*i*PrOH 90:10): $t_R=9.6$ min, $k=1.7$; *rac*: $t_R=10.6/15.8$ min, $k=1.9/3.3$, $\alpha=1.7$.

(±)-(1a*S*,7b*S*,11a*R*)-10-Benzyl-11a-hydroxy-1,9,10,11a-tetrahydro-1a*H*-pyrido[4′,3′:2,3]cyclobuta[1,2-*c*]quinoline-2,11(3*H*,8*H*)dione (17): Cyclobutane photoproduct **16** (110 mg, 199 μmol) was stirred in 10 vol % TFA in CH_2Cl_2 (10 mL) for 1.0 h at RT. Sat. aqueous $NaHCO_3$ (15 mL) was added and the mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated to yield the *N*-Boc deprotected aminoester (90 mg, quant) as a yellow foam which was used without further purification. This aminoester was refluxed in PhMe (10 mL) for 18 h. After evaporation of the solvent and purification of the residue by flash chromatography (2.0×5 cm, CH_2Cl_2/MeOH 20:1), hydroxylactam **17** (54 mg, 155 μmol, 78 %) was obtained as a white, crystalline solid. $R_f=0.20$ (EtOAc, [UV]); m.p. 195–197 °C; ^1H NMR (360 MHz, $CDCl_3$): $\delta=8.93$ (br, 1H, NH), 7.42–7.29 (m, 5H, H_{ar}), 7.25–7.17 (m, 2H, H_{ar}), 7.06 (virt. t, $^3J=7.4$ Hz, 1H, H_6), 6.81 (d, $^3J=7.9$ Hz, 1H, H_4), 4.79 (d, $^2J=14.5$ Hz, 1H, CH*H*Ph), 4.68 (d, $^2J=14.5$ Hz, 1H, C*H*HPh), 4.33 (br, 1H, OH), 3.68 (ddd, $^2J=13.3$, $^3J=12.9$, $^3J=3.0$ Hz, 1H, CH*H*N), 3.37 (ddd, $^2J=13.3$, $^3J=5.3$, $^3J=2.0$ Hz, 1H, C*H*HN), 3.08 (dd, $^3J=10.2$, $^3J=8.8$ Hz, 1H, C_{1a}H), 2.88 (dd, $^2J=12.8$, $^3J=10.2$ Hz, 1H, CHH_{exo}), 2.58 (dd, $^2J=12.8$, $^3J=8.8$ Hz, 1H, CH_{endo}H), 2.18 (ddd, $^2J=13.8$, $^3J=12.9$, $^3J=5.3$ Hz, 1H, RCH*H*), 1.93 ppm (ddd, $^2J=13.8$, $^3J=3.0$, $^3J=2.0$ Hz, 1H, RC*H*H); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta=172.9$ (s, CO), 169.9 (s, CO), 136.2 (s, C_{1Bn}/C_{3a}), 136.1 (s, C_{1Bn}/C_{3a}), 129.5 (d, C_{ar}H), 129.0 (d, C_{Bn}H), 128.7 (d, C_{ar}H), 128.1 (d, C_{ar}H), 128.0 (d, C_{Bn}H), 123.2 (d, C_6H), 120.5 (s, C_{7a}), 116.1 (d, C_4H), 72.9 (s, C_{11a}OH), 51.6 (t, CH_2Ph), 49.3 (s, C_{7b}), 43.2 (t, CH_2N), 40.5 (t, C_1HH), 32.8 (d, C_{1a}H), 32.4 ppm (t, RCH_2); IR (KBr): $\tilde{\nu}=3205$ (s, br, OH), 3060 (w, C_{ar}H), 2918 (w, C_{al}H), 1666 (vs, CONH), 1633 (vs, CONBn), 1594(s), 1493 (s), 1405 (m), 1194 (m), 755 (m), 701 cm^{-1} (m); MS (70 eV): *m*/*z* (%): 348 (2) [M^+], 320 (91) [$M-CO^+$], 265 (30), 159 (29) [RCH$_3^+$], 120 (19) [BnNCH$_2^+$], 91 (100) [C$_7$H$_7^+$], 40 (37); HRMS (70 eV): *m*/*z*: calcd for $C_{20}H_{20}N_2O_2$: 320.1525 [$M-CO^+$], found 320.1527.

(+)-*N*-2-[(3a*S*,9b*R*)-2-Hydroxy-1,4-dioxo-1,3a,4,5-tetrahydro-9b*H*-cyclopenta[*c*]quinoline-9-yl]ethyl-*N*-benzyl-*tert*-butylcarbamate (21): Cyclobutane photoproduct **16** (5.53 g, 10.0 mmol) was dissolved in MeOH (60 mL), 0.5 g K_2CO_3 added, and the mixture stirred at RT for 6.0 h. Sat. aqueous NH_4Cl (250 mL) was added, the MeOH evaporated and the aqueous residue extracted with EtOAc (1×100 mL + 2×50 mL). The combined organic phases were washed with H_2O (100 mL) and brine (100 mL), dried over Na_2SO_4, filtered and concentrated to give enone **21** (4.38 g, 9.77 mmol, 98 %) as a light yellow foam. Additional purification by flash chromatography was ineffective. $R_f=0.58$ (EtOAc, [UV]); ^1H NMR (360 MHz, $CDCl_3$, 60 °C): $\delta=9.35$ (s, 1H, NH), 7.62 (d, $^3J=7.8$ Hz, 1H, H_9), 7.30–7.19 (m, 4H, H_{ar}), 7.12–7.05 (m, 3H, H_{ar}), 6.82 (d, $^3J=7.9$ Hz, 1H, H_5), 6.63 (d, $^3J=3.1$ Hz, 1H, H_3), 4.34 (d, $^2J=15.2$ Hz, 1H, CH*H*Ph), 4.27 (d, $^2J=15.2$ Hz, 1H, C*H*HPh), 3.68 (brm, 1H, H_{al}), 3.20 (brm, 1H, H_{al}), 2.87 (virt. t, $J_t=10.6$ Hz, 1H, H_{al}), 2.33 (virt. dt, $J_t=12.2$, $J_d=4.3$ Hz, 1H, H_{al}), 1.84 (brm, 1H, H_{al}), 1.45 ppm [s, 9H, C(CH$_3$)$_3$]; ^{13}C NMR (90 MHz, $CDCl_3$, 60 °C): $\delta=202.8$ (s, CO), 169.0 (s, CONH), 155.8 (s, CO_{Boc}), 153.1 (s, C_2OH), 138.3 (s, C_{ar}), 135.6 (s, C_{ar}), 129.1 (d, C_{ar}H), 128.9 (d, C_{ar}H), 128.3 (d, C_{ar}H), 128.1 (d, C_{ar}H), 127.7 (d, C_{ar}H), 124.6 (d, C_8H), 119.2 (s, C_{9a}), 116.2 (d, C_6H), 80.7 [s, *C*(CH$_3$)$_3$], 51.1 (brt, CH_2Ph), 50.7 (s, C_{9b}), 47.7 (d, C_{3a}H), 43.2 (brt, CH_2N), 38.5 (brt, RCH_2), 28.8 ppm [q, C(*C*H$_3$)$_3$]; (d, C_3H) is not visible due to superimposition; IR (KBr): $\tilde{\nu}=3243$ (s, br, NH), 2976 (m, C_{al}H), 2926 (w, C_{al}H), 1673 (vs, CO), 1593 (m), 1494 (m), 1245 (w), 1163 (s), 756 (m), 700 cm^{-1} (m, CH_{Bn}); MS (70 eV): *m*/*z* (%): 448 (2) [M^+], 492 (18) [$M-t$Bu$^+$], 348 (100) [$M-$Boc$^+$], 214 (23), 120 (49) [BnNCH$_2^+$], 107 (36), 91 (73) [C$_7$H$_7^+$], 57 (77) [*t*Bu$^+$]; HRMS (70 eV): *m*/*z*: calcd for $C_{26}H_{28}N_2O_5$: 448.1998 [M^+], found 448.1985.

Enantiopure: According to the above procedure, enantiomerically pure enone (+)-**21** (340 mg, 758 μmol, quant.) was obtained in >99% *ee* when starting from enantiomerically pure cyclobutane (−)-**16**. $[\alpha]_D^{20}=+60$ ($c=1.0$ in CH_2Cl_2); chiral HPLC (Chiralpak AD, *n*-hexane/*i*PrOH 70:30): $t_R=6.9$ min; *rac*: $t_R=7.2/13.0$ min, $k=1.0/2.6$, $\alpha=2.6$.

(+)-(2a*S*,8b*R*,11a*S*)-11-Benzyl-11a-hydroxy-2,2a,9,10,11,11a-hexahydro-1*H*-pyrrolo[3′,2′:2,3]cyclopenta[1,2-*c*]quinoline-1,3(4*H*)-dione (18): Enone **21** (250 mg, 557 μmol) was stirred in 10 vol% TFA in CH_2Cl_2 (10 mL) for 1.5 h at RT. The mixture was diluted with CH_2Cl_2 (20 mL) and H_2O (20 mL) and made basic with 15% aqueous NaOH. The resulting suspension is adjusted to pH 8–10 with sat. aqueous NH_4Cl, phases were separated, and the aqueous phase extracted with CH_2Cl_2 (3×25 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent evaporated to give hemiaminal **18** (192 mg, 551 μmol, 99%) as a light yellow, crystalline solid. Attempted flash chromatography was ineffective and led to widespread decomposition. $R_f=0.55$ (EtOAc, [UV]); m.p. 166–169 °C (decomp); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=9.43$ (s, 1H, NH), 7.99 (d, $^3J=7.6$ Hz, 1H, H_8), 7.37–7.32 (m, 2H, H_{Bn}), 7.31–7.24 (m, 4H, H_{Bn}, H_6), 7.11 (t, $^3J=7.6$ Hz, 1H, H_7), 6.88 (d, $^3J=7.7$ Hz, 1H, H_5), 4.00 (d, $^2J=14.2$ Hz, 1H, CH*H*Ph), 3.70 (d, $^2J=14.2$ Hz, 1H, C*H*HPh), 3.58 (s, 1H, OH), 3.35 (virt. t, $^3J=9.4$ Hz, 1H, H_{2a}), 3.25–3.15 (m, 1H, CH*H*N), 3.21 (dd, $^2J=19.2$, $^3J=9.0$ Hz, 1H, C_2HH), 3.09 (ddd, $^2J=10.2$, $^3J=10.5$, $^3J=4.0$ Hz, 1H, C*H*HN), 2.52 (dd, $^2J=19.2$, $^3J=9.6$ Hz, 1H, C_2HH), 2.41 (ddd, $^2J=12.5$, $^3J=8.6$, $^3J=4.0$ Hz, 1H, RCH*H*), 2.27 ppm (ddd, $^2J=12.5$, $^3J=10.5$, $^3J=7.3$ Hz, 1H, RC*H*H); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta=208.6$ (s, CO), 170.9 (s, CONH), 138.5 (s, C_{1Bn}), 136.1 (s, C_{4a}), 130.8 (d, C_8H), 128.7 (d, C_{ar}H), 128.4 (d, C_{Bn}H), 127.9 (d, C_{Bn}H), 127.1 (d, C_{ar}H), 123.9 (d, C_7H), 121.3 (s, C_{8a}H), 115.8 (d, C_5H), 96.7 (s, C_{11a}), 56.6 (s, C_{8b}), 50.3 (t, CH_2Ph), 49.5 (t, CH_2N), 43.4 (d, C_{2a}H), 37.9 (t, C_2HH), 37.4 ppm (t, RCH_2); IR (KBr): $\tilde{\nu}=3440$ (vs, br, OH), 3059 (m, C_{ar}H), 2913 (m, C_{al}H), 2880 (m, C_{al}H), 1743 (vs, CO), 1690 (vs, CON), 1588 (m), 1491 (s), 1420 (s), 1132 (m), 738 (m), 699 (m), 509 cm^{-1} (m); MS (70 eV): *m*/*z* (%): 348 (1) [M^+], 330 (12), 320 (82) [$M-CO^+$], 305 (11) [$M-COOH^+$] 289 (17), 265 (34), 91 (100) [$C_7H_7^+$]; HRMS (70 eV): *m*/*z*: calcd for $C_{21}H_{20}N_2O_3$: 348.1474 [M^+], found 348.1481; elemental analysis calcd (%) for $C_{21}H_{20}N_2O_3$: C 72.40, H 5.79; found: C 72.30, H 5.78.

(+)-(3a*S*,9b*R*)-9b-2-[Benzyl(*tert*-butoxycarbonyl)amino]ethyl-1,4-dioxo-3a,4,5,9b-tetrahydro-1*H*-cyclopenta[*c*]quinoline-2-yl acetate (22): Enone **21** (2.63 g, 5.86 mmol) and NEt_3 (1.14 mL, 830 mg, 8.20 mmol, 1.40 equiv) were dissolved in THF (40 mL), cooled to 0 °C, treated dropwise with acetyl chloride (0.48 mL, 529 mg, 6.74 mmol, 1.15 equiv) and stirred at 0 °C for 30 min. H_2O (100 mL) was added, the THF evaporated and the aqueous residue extracted with EtOAc (3×100 mL). The combined organic extractes were dried over Na_2SO_4, filtered and concentrated. After purification of the crude product by flash chromatography (5.0×15 cm, P/EtOAc 1:1→2:3), enolacetate **22** (2.73 g, 5.57 mmol, 95%) was obtained as a light yellow foam. $R_f=0.35$ (P/EtOAc 1:1, [UV]); ^{1}H NMR (360 MHz, $CDCl_3$, 60 °C): $\delta=8.94$ (br., 1H, NH), 7.60 (brm, 1H, H_9), 7.47 (br., 1H, H_3), 7.30–7.15 (m, 4H, H_{ar}), 7.14–7.02 (m, 3H, H_{ar}), 6.74 (brm, 1H, H_6), 4.40–4.20 (m, 2H, CH_2Ph), 3.82 (br, 1H, H_{al}), 3.20 (br, 1H, H_{al}), 2.88 (br., 1H, H_{al}), 2.31 (br, 1H, H_{al}), 2.21 (s, 3H, CH_3), 1.88 (br., 1H, H_{al}), 1.44 ppm [br, 9H, $C(CH_3)_3$]; ^{13}C NMR (90 MHz, $CDCl_3$, 60 °C): $\delta=199.2$ (s, CO), 166.9* (s, CO_{Ac}), 166.8* (s, CONH), 155.3 (s, CO_{Boc}), 149.5 (s, C_2OAc), 141.6 (d, C_3H), 138.1* (s, C_{5a}), 135.2* (s, C_{1Bn}), 128.8 (d, C_{ar}H), 128.5 (d, C_{ar}H), 128.1 (d, C_{ar}H), 127.8 (brd, C_{ar}H), 127.4 (d, C_{ar}H), 124.3 (d, C_{ar}H), 119.2 (s, C_{9a}), 115.7 (d, C_6H), 80.2 [s, O*C*-$(CH_3)_3$], 50.8 (brd, CH_2Ph), 50.5 (s, C_{9b}), 48.4 (d, C_{3a}H), 42.8 (t, CH_2N), 38.1 (t, RCH_2), 28.5 [q, OC(CH_3)$_3$], 20.5 ppm (q, CH_3); broad signals due to Boc coalescence; IR (KBr): $\tilde{\nu}=3229$ (m, br, CONH), 3064 (w, C_{ar}H), 2977 (m, C_{al}H), 1780 (s, CO), 1730 (s, CO), 1680 (vs, CONH), 1594 (m), 1367 (m), 1188 (m), 1042 (m), 757 (m), 701 cm^{-1} (m); MS (70 eV): *m*/*z* (%): 490 (2) [M^+], 434 (14) [$M-t$Bu$^+$], 417 (7), 390 (78) [$M-$Boc$^+$], 345 (25) [$M-$Boc$-$Ac$^+$], 120 (62) [BnNHCH_2^+], 107 (36), 91 (100) [$C_7H_7^+$], 57 (7) [tBu$^+$], 43 (25) [Ac$^+$]; HRMS (70 eV): *m*/*z*: calcd for $C_{28}H_{30}N_2O_6$: 490.2104 [M^+], found 490.2112.

Enantiopure: According to the above procedure, enantiomerically pure enolacetate (+)-**22** (353 mg, 720 μmol, 95%) was obtained in >99% *ee* when starting from enantiomerically pure enone (+)-**21**. $[\alpha]_D^{20}=+28.9$ ($c=1.0$ in CH_2Cl_2); chiral HPLC (Chiralpak AS-H, *n*-hexane/*i*PrOH 80:20): $t_R=11.4$ min, $k=2.3$; *rac*: $t_R=14.2/19.6$ min, $k=2.3/3.6$, $\alpha=1.6$.

(±)-(1*R*,2*R*,11*R*,15*S*)-14-Benzyl-3,16-dioxo-4,14-diazatetracyclo-[9.3.2.0^{2,11}.0^{5,10}]hexadeca-5,7,9-trien-15-yl acetate (23): Enolacetate **22** (50 mg, 102 μmol) was stirred in 7.5 vol% TFA in CH_2Cl_2 (5 mL) for 2.0 h at RT. The mixture was diluted with CH_2Cl_2 (20 mL) and H_2O (20 mL) and made basic with 5% aqueous NaOH. Brine (50 mL) was added, phases were separated, and the aqueous phase extracted with CH_2Cl_2 (3×30 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent evaporated to give acetate **23** (38 mg, 97 μmol, 95%) as an off-white solid. Attempted purification by flash chromatography led to significant losses (60–70%) of product but no improvement of product purity. $R_f=0.37$ (P/EtOAc 1:1, [UV]); m.p. 175–177 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=8.83$ (brs, 1H, NH), 7.32 (d, $^3J=7.4$ Hz, 1H, H_9), 7.28–7.22 (m, 4H, $H_{2/3Bn}$), 7.21–7.16 (m, 2H, H_7, H_{4Bn}), 7.06 (t, $^3J=7.6$ Hz, 1H, H_8), 6.75 (d, $^3J=7.7$ Hz, 1H, H_6), 5.40 (d, $^3J=5.5$ Hz, 1H, CHOAc), 4.54 (d, $^3J=5.5$ Hz, 1H, CHN), 4.04 (d, $^2J=13.6$ Hz, 1H, CH*H*Ph), 3.79 (d, $^2J=13.6$ Hz, 1H, CH*H*Ph), 3.17 (s, 1H, C_2H), 2.91 (dd, $^2J=12.9$, $^3J=6.3$ Hz, 1H, CH*H*N), 2.75 (ddd, $^2J=12.9$, $^3J=12.9$, $^3J=4.0$ Hz, 1H, C*H*HN), 2.41 (dd, $^2J=12.4$, $^3J=4.0$ Hz, 1H, RCH*H*), 2.19 (s, 3H, CH_3), 1.96 ppm (ddd, $^3J=12.9$, $^2J=12.4$, $^3J=6.3$ Hz, 1H, RC*H*H); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta=211.1$ (s, CO), 169.4 (s, CONH/CO_{Ac}), 167.9 (s, CONH/CO_{Ac}), 138.8 (s, C_5/C_{1Bn}), 135.6 (s, C_5/C_{1Bn}), 129.2 (d, C_{ar}H), 128.4 (d, C_{ar}H), 128.3 (d, C_{ar}H), 127.3 (d, C_{ar}H), 126.7 (d, C_{ar}H), 124.0 (d, C_8H), 121.1 (s, C_{10}), 115.9 (d, C_6H), 77.3 (d, CHO), 60.6 (t, CH_2Ph), 60.3 (d, CHN), 51.7 (s, C_{11}), 48.4 (d, C_2H), 44.5 (t, CH_2N), 35.7 (t, RCH_2), 20.7 ppm (q, CH_3); IR (KBr): $\tilde{\nu}=3447$ (w, br, NH), 3198 (m), 3069 (w, C_{ar}H), 2908 (m, C_{al}H), 1757 (vs, CO), 1672 (vs, CO), 1591 (m), 1490 (s), 1369 (s), 1274 (s), 753 (m), 700 cm^{-1} (w); MS (70 eV): *m*/*z* (%): 390 (43) [M^+], 347 (64) [$M-$Ac$^+$], 330 (6) [$M-$AcOH$^+$], 289 (24), 199 (27), 167 (28), 149 (55), 91 (100) [$C_7H_7^+$], 57 (24) [tBu$^+$], 43 (28) [Ac$^+$]; HRMS (70 eV): *m*/*z*: calcd for $C_{23}H_{22}N_2O_4$: 390.1580 [M^+], found 390.1578.

(+)-(1*S*,2a*S*,8b*R*,11a*R*)-1-(Acetyloxy)-3-oxo-1,2,2a,3,4,9,10,11a-octahydro-11*H*-pyrrolo[3′,2′:2,3]cyclopenta[1,2-*c*]quinoline-11-*tert*-butylcarboxylate (28): Enolacetate **22** (346 mg, 705 μmol) was stirred in 10 vol% TFA in CH_2Cl_2 (15 mL) for 1.0 h at RT. The solution was concentrated, redissolved in MeOH (120 mL) and cooled to 0 °C. Pd(OH)$_2$/C (300 mg 10–15% Pd with 50% H_2O, ≥141 μmol Pd, 20 mol%) was added, and the solution was stirred under a H_2 atmosphere (1 bar) for 18 h while slowly warming to RT. After removal of the catalyst by filtration and evaporation of the solvent, the remaining crude TFA salt was suspended in CH_2Cl_2 (25 mL), the solution adjusted to pH 9–10 with NEt_3, Boc_2O (200 mg, 917 μmol, 1.3 equiv) was added and the mixture was stirred at RT for 1.0 h. Sat. aqueous NH_4Cl (40 mL) and H_2O (40 mL) were added, phases were separated and the aqueous phase extracted with CH_2Cl_2 (5×30 mL). The combined organic phases were dired over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography (2.5×20 cm, P/EtOAc 1:1→EtOAc) to give acetate **28** (212 mg, 549 μmol, 78%) as a white solid. $R_f=0.50$ (EtOAc, [UV]); m.p. 130–138 °C (polymorph), 200–203 °C (decomp); ^{1}H NMR (360 MHz, $CDCl_3$): $\delta=9.21$ (s, 1H, NH), 7.32 (d, $^3J=7.5$ Hz, 1H, H_8), 7.22 (t, $^3J=7.5$ Hz, 1H, H_6), 7.10 (t, $^3J=7.3$ Hz, 1H, H_7), 6.84 (d, $^3J=7.9$ Hz, 1H, H_5), 5.16 (brm, 1H, CHOAc), 4.41/4.27 (br, 1H, CHN), 3.92/3.86 (brm, 1H, CH*H*N), 3.47 (brm, 1H, C*H*HN), 2.90 (brm, 1H, C_{2a}H), 2.61 (brm, 1H, CH*H*), 2.25–2.10 (m, 3H, C*H*H, RCH_2), 1.83 (s, 3H, CH_3), 1.46 ppm [brs, 9H, $C(CH_3)_3$]; ^{13}C NMR (90 MHz, $CDCl_3$): $\delta=170.7$ (s, CO_{Ac}), 169.6 (brs, CONH), 153.7 (s, CO_{Boc}), 135.1 (s, C_{4a}), 128.3 (d, C_6H), 127.1 (d, C_8H), 125.5 (brs, C_{8a}), 124.3 (d, C_7H), 115.9 (d, C_5H), 80.5 [brs, *C*-$(CH_3)_3$], 79.1 (brd, CHOAc), 75.4 (d, CHN), 56.2 (brs, C_{8b}), 47.7 (d, C_{2a}H), 46.1 (brt, CH_2N), 39.1 (brt, RCH_2), 36.5 (t, C_2HH), 28.4 [q, C-(CH_3)$_3$], 20.8 ppm (q, CH_3); IR (KBr): $\tilde{\nu}=3448$ (s, br, CONH), 2977 (m, C_{al}H), 2931 (w, C_{al}H), 1743 (s, CO), 1686 (vs, CONH), 1391 (s, CH_3), 1240 (s, COOMe), 1167 (m), 1042 (m), 758 cm^{-1} (m); MS (70 eV): *m*/*z* (%): 386 (2) [M^+], 326 (24) [$M-$AcOH$^+$], 270 (100) [$M-$AcO$-t$Bu$^+$], 226 (26) [$M-$AcOH$-$Boc$^+$], 173 (19), 57 (81) [tBu$^+$], 44 (13) [Ac$^+$], 41 (14) [$C_3H_5^+$]; HRMS (70 eV): *m*/*z*: calcd for $C_{21}H_{26}N_2O_5$: 386.1842 [M^+], found 386.1883.

Enantiopure: According to the above procedure, enantiomerically pure acetate (+)-**28** (270 mg, 700 μmol, 76%) was obtained as a white foam with >99% *ee* when starting from enantiomerically pure enolacetate (+)-**22**. $[\alpha]_D^{20}=+23.4$ ($c=1.0$ in CH_2Cl_2); chiral HPLC (Chiralpak AD-H, *n*-hexane/*i*PrOH 80:20): $t_R=11.7$ min, $k=2.4$; *rac*: $t_R=14.8/17.3$ min, $k=2.4/3.0$, $\alpha=1.25$.

(+)-(1*S*,2a*S*,8b*R*,11a*R*)-1-Hydroxy-3-oxo-1,2,2a,3,4,9,10,11a-octahydro-11*H*-pyrrolo[3′,2′:2,3]cyclopenta[1,2-*c*]quinoline-11-*tert*-butylcarboxylate (29): Acetate **28** (206 mg, 533 μmol) was stirred in K_2CO_3 in MeOH (25 mL) for 3.5 h at RT. After evaporation of the solvent, the residue was filtered through a short plug of silica (3.5×5 cm, CH_2Cl_2/MeOH 15:1) and concentrated to give the free alcohol **29** (173 mg, 502 μmol, 94%) as a white, crystalline solid. $R_f=0.55$ (CH_2Cl_2/MeOH 10:1, [UV]); m.p. 114–115°C (decomp); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=9.49$ (s, 1H, NH), 7.31 (d, $^3J=7.4$ Hz, 1H, H_8), 7.18 (t, $^3J=7.3$ Hz, 1H, H_6), 7.08 (t, $^3J=7.4$ Hz, 1H, H_7), 6.85 (d, $^3J=7.7$ Hz, 1H, H_5), 4.31 (d, $^3J=3.8$ Hz, 0.65H*, CHNBoc), 4.20 (brm, 0.35H*, CHNBoc), 4.11 (virt. dt, $^3J_t=10.4$, $^3J_d=3.8$ Hz, 1H, C*H*OH), 3.90/3.77 (brm, 0.35H*/0.65H*, CH*H*N), 3.76 (brs, <1H, OH), 3.43 (ddd, $^{3/2}J=10.5$, $^{3/2}J=10.4$, $^3J=6.9$ Hz, 1H, C*H*HN), 2.81 (dd, $^3J=11.8$, $^3J=6.3$ Hz, 1H, H_{2a}), 2.48 (virt. dt, $^2J=12.1$, $^3J=6.0$ Hz, 1H, CH*H*), 2.12 (ddd, $^2J=13.2$, $^3J=6.7$, $^3J=2.8$ Hz, 1H, RCH*H*), 2.08–1.88 (m, 2H, C*H*H, RC*H*H), 1.51 ppm [s, 9H, $C(CH_3)_3$]; *signals are doubled due to Boc coalescence; ^{13}C NMR (63 MHz, $CDCl_3$): $\delta=$ 170.9 (s, CONH), 155.4 (s, CO_{Boc}), 134.7 (s, C_{4a}), 128.1 (d, C_6H), 127.3 (d, C_8H), 126.8 (s, C_{8a}), 124.4 (d, C_7H), 116.0 (d, C_5H), 80.6 [s, $C(CH_3)_3$], 79.0 (d, CHNBoc), 78.9 (d, C*H*OH), 55.1 (s, C_{8b}), 47.3 (d, $C_{2a}H$), 46.3 (t, CH_2N), 40.1 (t, RCH_2), 37.9 (t, C_2HH), 28.4 ppm [q, $C(CH_3)_3$]; IR (KBr): $\tilde{\nu}=3422$ (vs, br, OH), 2973 (w, $C_{al}H$), 2927 (w, $C_{al}H$), 1680 (vs, C=O), 1657 (vs, C=ONH), 1594 (m, C_{ar}), 1402 (vs, CH_3), 1169 (m, C–O), 1117 (m, C–O), 903 (w), 754 (m, C_{ar}), 730 cm^{-1} (m, C_{ar}); MS (70 eV): *m*/*z* (%): 344 (36) [M^+], 288 (55) [$M-t$Bu$^+$], 243 (29) [$M-$Boc$^+$], 215 (26), 159 (20) [RCH_3^+], 144 (17), 84 (21), 57 (100) [tBu$^+$], 41 (17) [$C_3H_5^+$]; HRMS (70 eV): *m*/*z*: calcd for $C_{19}H_{24}N_2O_4$: 344.1736 [M^+], found 344.1733; elemental analysis calcd (%) for $C_{19}H_{24}N_2O_4$: C 66.26, H 7.02; found: C 66.30, H 6.93.

Enantiopure: According to the above procedure, enantiomerically pure alcohol (+)-**29** (405 mg, 1.18 mmol, 96%) was obtained as a white foam with >99% *ee* when starting from enantiomerically pure acetate (+)-**28**. $[\alpha]_D^{20}=+26.0$ ($c=1.0$ in CH_2Cl_2); chiral HPLC (Chiralpak AD-H, *n*-hexane/*i*PrOH 70:30): $t_R=9.1$ min, $k=1.8$; *rac*: $t_R=11.6/14.6$ min, $k=1.7/2.4$, $\alpha=1.4$.

(+)-(2a*S*,8b*R*,11a*R*)-1,3-Dioxo-1,2,2a,3,4,9,10,11a-octahydro-11*H*-pyrrolo[3′,2′:2,3]cyclopenta[1,2-*c*]quinoline-11-*tert*-butylcarboxylate (30): Alcohol **29** (178 mg, 517 μmol) and IBX (434 mg, 1.55 mmol, 3.0 equiv) were stirred in DMSO (7.5 mL) for 30 h at RT. H_2O (150 mL) and sat. aqueous $NaHCO_3$ (30 mL) were added and the mixture extracted once with EtOAc (100 mL). The organic extract was washed with H_2O (3×100 mL) and brine (2×100 mL), dried over Na_2SO_4 and filtered. After removal of the solvent, ketone **30** (167 mg, 488 μmol, 94%) was obtained as a white, crystalline solid, which sometimes contained an additional $^1/_2$ equiv of co-crystallized EtOAc. $R_f=0.48$ (EtOAc, [UV]); m.p. 196–199°C (decomp); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=9.74$ (br, 1H, NH), 7.35–7.20 (m, 2H, $C_{ar}H$), 7.10 (t, $^3J=7.2$ Hz, 1H, H_7), 6.92 (d, $^3J=7.7$ Hz, 1H, H_5), 4.46/4.25 (br, 1H, CHN), 3.94 (brm, 1H, CH*H*N), 3.49 (ddd, $^2J=11.5$, $^3J=8.1$, $^3J=7.7$ Hz, 1H, C*H*HN), 3.17 (virt. t, $^3J=8.6$ Hz, 1H, $C_{2a}H$), 2.88 (virt. d, $^3J=8.6$ Hz, 2H, C_2HH), 2.32–2.10 (m, 2H, RCH_2), 1.46 ppm [brs, 9H, $C(CH_3)_3$]; ^{13}C NMR (63 MHz, $CDCl_3$): $\delta=209.3$ (brs, CO), 170.2 (s, CONH), 154.5 (s, CO_{Boc}), 135.3 (s, C_{4a}), 129.0 (d, C_6H), 126.8 (d, C_8H), 124.5 (d, C_7H), 124.0 (s, C_{8a}), 116.2 (d, C_5H), 80.7 [s, *C*-$(CH_3)_3$], 70.6 (brd, CHN), 52.8 (brs, C_{8b}), 46.1 (brt, CH_2N), 42.4 (d, $C_{2a}H$), 39.3 (t, C_2H), 37.5 (brt, RCH_2), 28.2 ppm [q, $C(CH_3)_3$]; signal broadening due to Boc coalescence; IR (KBr): $\tilde{\nu}=3204$ (w, br, CONH), 3067 (w, $C_{ar}H$), 2979 (m, $C_{al}H$), 2929 (m, $C_{al}H$), 1756 (s, C=O), 1678 (vs, br, CON), 1592 (m, C_{ar}), 1493 (s), 1392 (vs, CH_3), 1245 (m), 1170 (s, C–O), 754 cm^{-1} (s, C_{ar}); MS (70 eV): *m*/*z* (%): 342 (18) [M^+], 286 (49) [$M-t$Bu$^+$], 269 (13) [$M-t$BuO$^+$], 242 (15) [$M-$Boc+H$^+$], 214 (25), 159 (77) [RCH_3^+], 57 (100) [tBu$^+$]; HRMS (70 eV): *m*/*z*: calcd for $C_{19}H_{22}N_2O_4$: 342.1580 [M^+], found 342.1580.

Enantiopure: According to the above procedure, enantiomerically pure ketone (+)-**30** (66 mg, 193 μmol, 95%) was obtained as a white foam with >99% *ee* when starting from the enantiomerically pure alcohol (+)-**29**. $[\alpha]_D^{20}=+123$ ($c=1.0$ in CH_2Cl_2); chiral HPLC (Chiralpak AD-H, *n*-hexane/*i*PrOH 50:50): $t_R=6.1$ min, $k=0.7$; *rac*: $t_R=7.3/10.7$ min, $k=0.9/1.7$, $\alpha=1.9$.

(+)-(2a*S*,8b*R*,11a*S*)-1-[(*E*)-2-Ethoxy-2-oxoethyliden]-3-oxo-1,2,2a,3,4,9,10,11a-octahydro-11*H*-pyrrolo[3′,2′:2,3]cyclopenta[1,2-*c*]quinoline-11-*tert*-butylcarboxylate (31): Ketone **30** (1.50 g, 4.38 mmol) and the Wittig reagent PH_3P=CHCOOEt (1.98 g, 5.69 mmol, 1.30 equiv) were refluxed in THF (75 mL) for 20 h. After removal of the solvent, the residue was purified by flash chromatography (5.0×25 cm, P/EtOAc 1:1→1:2) to give the α,β-unsaturated ester **31** (1.52 g, 3.68 mmol, 84%) as a white crystalline solid. $R_f=0.60$ (EtOAc, [UV]); m.p. 190–193°C (decomp); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=9.34/9.18$ (br., 1H, NH), 7.30–7.14 (brm, 2H, H_6, H_8), 7.07 (t, $^3J=7.3$ Hz, 1H, H_7), 6.86 (d, $^3J=7.7$ Hz, 1H, H_5), 6.41/6.19 (brm, 1H, =CH), 4.98/4.74 (brm, 1H, CHN), 4.12–3.81 (brm, 3H, OCH_2, H_{al}), 3.72–3.40 (brm, 2H, H_{al}), 3.35–2.95 (m, 2H, H_{al}), 2.20–2.00 (brm, 2H, RCH_2), 1.48 [brs, 9H, $(CH_3)_3$], 1.25 ppm (t, $^3J=7.1$ Hz, 3H, CH_3); signal doubling and strong broadening due to Boc coalescence; ^{13}C NMR (63 MHz, $CDCl_3$): $\delta=171.0$ (s, CONH), 166.3 (brs, COOEt), 159.3 (brs, C_1), 154.8/154.4 (brs, CO_{Boc}), 135.6 (s, C_{4a}), 128.6 (d, C_6H), 126.7 (brd, C_8H), 124.5 (brs, C_{8a}), 124.1 (d, C_7H), 118.9/118.2 (brd, =CH), 116.0 (d, C_5H), 80.8/80.4 [brs, $C(CH_3)_3$], 72.8/72.4 (brd, CHN), 60.0 (t, OCH_2), 55.3/55.0 (brs, C_{8b}), 46.6 (brd, $C_{2a}H$), 46.1 (brt, CH_2N), 37.9/37.1 (brt, RCH_2), 35.5/34.9 (brt, C_2HH), 28.4 [q, $C(CH_3)_3$], 14.2 (q, CH_3); signal doubling and strong broadening due to Boc coalescence; IR (KBr): $\tilde{\nu}=$ 3412 (w, br, CONH), 3066 (w, $C_{ar}H$), 2978 (m, $C_{al}H$), 1687 (vs, br, CO), 1593 (m, C_{ar}), 1490 (s), 1390 (vs, CH_3), 1210 (s), 1165 (s, C–O), 1034 (m), 755 cm^{-1} (s, C_{ar}); MS (70 eV): *m*/*z* (%): 412 (5) [M^+], 356 (40) [$M-t$Bu$^+$], 312 (49) [$M-$Boc$^+$], 283 (25), 266 (25) [$M-$Boc$-$OEt$^+$], 239 (19) [$M-$Boc$-$COOEt$^+$], 159 (21) [RCH_3^+], 57 (100) [tBu$^+$]; HRMS (70 eV): *m*/*z*: calcd for $C_{23}H_{28}N_2O_5$: 412.1998 [M^+], found 412.1993; elemental analysis calcd (%) for $C_{23}H_{28}N_2O$: C 66.97, H 6.84; found: C 66.90, H 6.75.

Enantiopure: According to the above procedure, enantiomerically pure α,β-unsaturated ester (+)-**31** (157 mg, 381 μmol, 84%) was obtained as a white foam with >99% *ee* when starting from the enantiomerically pure ketone (+)-**30**. $[\alpha]_D^{20}=+46.1$ ($c=1.0$ in CH_2Cl_2); chiral HPLC (Chiralpak AD-H, *n*-hexane/*i*PrOH 80:20): $t_R=11.9$ min, $k=2.3$; *rac*: $t_R=12.8/14.9$ min, $k=2.3/3.0$, $\alpha=1.3$.

(+)-(2a*S*,8b*R*,11a*S*)-1-[(*E*)-2-Hydroxyethyliden]-3-oxo-1,2,2a,3,4,9,10,11a-octahydro-11*H*-pyrrolo[3′,2′:2,3]cyclopenta[1,2-*c*]quinoline-11-*tert*-butylcarboxylate (32): α,β-Unsaturated ester **31** (200 mg, 485 μmol) was dissolved in dry CH_2Cl_2 (20 mL), cooled to −45°C, treated dropwise with DIBAL-H (1.1 M in cyclohexane, 1.76 mL, 1.94 mmol, 4.0 equiv) and stirred at −45°C for 30 min. The reaction was quenched with a few drops of MeOH, and the mixture concentrated to dryness. After purification of the crude residue by flash chromatography (2.5×25 cm, CH_2Cl_2/MeOH 30:1→20:1), allylic alcohol **32** (145 mg, 391 μmol, 81%) was obtained as a white foam. $R_f=0.20$ (EtOAc, [UV]); ^{1}H NMR (360 MHz, $CDCl_3$): $\delta=$ 9.22 (brs, 1H, NH), 7.24 (brs, 1H, H_8), 7.19 (t, $^3J=7.6$ Hz, 1H, H_6), 7.06 (t, $^3J=7.5$ Hz, 1H, H_7), 6.84 (d, $^3J=7.7$ Hz, 1H, H_5), 6.13/5.97 (brs, 1H, =CH), 4.90/4.67 (brs, 1H, CHN), 4.12 (d, $^3J=5.2$ Hz, 2H, CH_2O), 4.05–3.80 (brm, 1H, C*H*HN), 3.43 (ddd, $^2J=16.1$, $^3J=11.8$, $^3J=7.9$ Hz, 1H, CH*H*N), 3.02–2.88 (m, 2H, $C_{2a}H$, C_2HH), 2.85–2.55 (brm, 1H, C_2HH), 2.10/1.95 (brm, 3H, RCH_2, OH), 1.48 ppm [s, 9H, $C(CH_3)_3$]; ^{13}C NMR (90 MHz, $CDCl_3$): $\delta=171.4$ (s, CONH), 154.6 (brs, CO_{Boc}), 140.7 (s, C_1), 135.4 (s, C_{4a}), 128.3 (d, C_6H), 127.1/126.9 (brd, =CH), 126.8 (brd, C_8H), 125.8/125.4 (brs, C_{8a}), 124.2 (d, C_7H), 115.8 (d, C_5H), 80.3/80.0 [brs, *C*-$(CH_3)_3$], 72.0/71.5 (brd, CHN), 60.4 (t, CH_2OH), 56.0/55.1 (brs, C_{8b}), 46.8 (d, $C_{2a}H$), 45.9 (brt, CH_2N), 38.5/38.0 (brt, RCH_2), 32.7/32.2 (brt, C_2HH), 28.5 ppm [q, $C(CH_3)_3$]; signal doubling and strong broadening due to Boc coalescence; IR (KBr): $\tilde{\nu}=3224$ (w, br., OH/NH), 2973 (w, $C_{al}H$), 2931 (w, $C_{al}H$), 1666 (vs, br., CO), 1592 (m, C_{ar}), 1488 (m), 1389 (s, br.), 1164 (m), 755 cm^{-1} (m, C_{ar}); MS (70 eV): *m*/*z* (%): 370 (4) [M^+], 352 (15) [$M-H_2O^+$], 314 (60), 296 (77) [$M-t$BuOH$^+$], 226 (82), 159 (35)

[RCH_3^+], 57 (100) [tBu$^+$], 41 (28) [$C_3H_5^+$]; HRMS (70 eV): m/z: calcd for $C_{21}H_{26}N_2O_4$: 370.1893 [M^+], found 370.1883.

Enantiopure: According to the above procedure, enantiomerically pure allylic alcohol (+)-**32** was obtained with >99% *ee* when starting from the enantiomerically pure α,β-unsaturated ester (+)-**31**. $[\alpha]_D^{20} = +64.8$ ($c = 1.0$ in CH_2Cl_2); chiral HPLC (Chiralpak AD-H, *n*-hexane/*i*PrOH 80:20): $t_R = 12.6$ min, $k = 2.7$; *rac*: $t_R = 15.2/30.2$ min, $k = 2.8/6.5$, $\alpha = 2.3$.

(±)-(2a*S*,8b*R*,11a*S*)-11-[(*Z*)-3-Iodo-2-propenyl]-3-oxo-2,2a,3,4,9,10,11,11a-octahydro-1*H*-pyrrolo[3′,2′:2,3]cyclopenta[1,2-*c*]quinoline-1-yliden-2-ethylacetate (33): α,β-Unsaturated ester **31** (75 mg, 182 μmol) was stirred in 20 vol% TFA in CH_2Cl_2 (2.0 mL) for 1.0 h at RT and the solution concentrated to dryness. The residue was dissolved in MeCN (2.0 mL), made basic with solid K_2CO_3 and treated with (*Z*)-3-bromo-1-iodopropene (22 μL, 55 mg, 222 μmol, 1.2 equiv) for 6.0 h at RT. H_2O (50 mL) was added and the mixture extracted with EtOAc (2×25 mL). The combined organic phases were washed with H_2O (15 mL) and brine (15 mL), dried over Na_2SO_4, filtered and the solvent evaporated to give vinyliodide **33** (80 mg, 167 μmol, 92%) as an off-white, crystalline solid. $R_f = 0.58$ (EtOAc, [UV]); m.p. 177–182 °C; ^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 8.08$ (br s, 1H, NH), 7.31 (d, $^3J = 7.5$ Hz, 1H, H_8), 7.18 (t, $^3J = 7.6$ Hz, 1H, H_6), 7.05 (t, $^3J = 7.6$ Hz, 1H, H_7), 6.74 (d, $^3J = 7.7$ Hz, 1H, H_5), 6.40 (d, $^3J = 7.7$ Hz, 1H, =CHI), 6.32 (virt. td, $^3J_t = 7.3$, $^3J_d = 4.8$ Hz, 1H, C*H*=CHI), 5.81 (virt. t, $^4J = 1.8$ Hz, 1H, =CH), 4.12 (q, $^3J = 7.1$ Hz, 2H, OCH_2), 3.67 (br s, 1H, CHN), 3.61–3.48 (m, 2H, NCH*H*, C_2H*H*), 3.42–3.32 (m, 2H, C_{2a}H, CH*H*N), 3.15 (dd, $^2J = 14.3$, $^3J = 7.0$ Hz, 1H, NC*H*H), 2.91–2.78 (m, 2H, C*H*HN, C_2*H*H), 2.31 (ddd, $^2J = 13.5$, $^3J = 8.1$, $^3J = 6.4$ Hz, 1H, RCH*H*), 1.88 (virt. td, $^{2/3}J_t = 11.7$, $^3J_d = 4.5$ Hz, 1H, RC*H*H), 1.24 ppm (t, $^3J = 7.1$ Hz, 3H, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 172.4$ (s, CONH), 165.8 (s, COOEt), 159.9 (s, C_1), 137.2 (d, H*C*=CHI), 136.2 (s, C_{4a}), 128.2 (d, C_6H), 126.9 (d, C_8H), 124.2 (s, C_{8a}), 124.0 (d, C_7H), 116.8 (d, =CH), 116.1 (d, C_5H), 83.6 (d, HC=*C*HI), 80.3 (d, CHN), 60.1 (t, OCH_2), 56.7 (s, C_{8b}), 56.1 (t, *C*H_2CH=), 53.6 (t, CH_2N), 50.0 (d, C_{2a}H), 37.9 (t, RCH_2), 36.7 (t, C_2HH), 14.2 ppm (q, CH_3); IR (KBr): $\tilde{\nu} = 3432$ (w, br., CONH), 3058 (w, C_{ar}H), 2975 (w, C_{al}H), 1712 (s, COOEt), 1675 (vs, CONH), 1592 (s, C_{ar}), 1490 (m), 1388 (m, CH_3), 1372 (m), 1209 (s), 1139 (m, C–O), 1035 (m), 754 (s, C_{ar}); MS (70 eV): m/z (%): 478 (16) [M^+], 449 (7) [$M-Et^+$], 433 (8) [$M-OEt^+$], 405 (10) [$M-COOEt^+$], 351 (27) [$M-I^+$], 311 (100) [$M-C_3H_4I^+$], 277 (62), 167 (19) [$C_3H_4I^+$]; HRMS (70 eV): m/z: calcd for $C_{21}H_{23}IN_2O_3$: 478.0754 [M^+], found 478.0755.

Single-crystal X-ray structure determination of compound (±)-33: Crystal data and details of the structure determination: formula: $C_{21}H_{23}IN_2O_3$; $M_r = 478.31$; crystal color and shape: colorless fragment, crystal dimensions = 0.53×0.56×0.58 mm; crystal system: triclinic; space group $P\bar{1}$ (no. 2); $a = 9.7252(11)$, $b = 9.8423(3)$, $c = 11.7678(15)$ Å; $\alpha = 76.621(6)$, $\beta = 70.268(11)$, $\gamma = 72.021(6)°$; $V = 998.3(2)$ Å^3; $Z = 2$; $\mu(Mo_{K\alpha}) = 1.627$ mm^{-1}; $\rho_{calcd} = 1.591$ g cm^{-3}; θ range = 2.67–25.36°; data collected: 21917; independent data [$I_o > 2\sigma(I_o)$/all data/R_{int}]: 3327/3640/0.016; data/restraints/parameters: 3640/0/246; $R1$ [$I_o > 2\sigma(I_o)$/all data]: 0.0268/0.0308; $wR2$ [$I_o > 2\sigma(I_o)$/all data]: 0.0601/0.0622; GOF = 1.054; $\Delta\rho_{max/min}$: 0.81/−0.75 e Å^{-3}.

CCDC 717011 (**33**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(−)-(6b*R*,11a*R*,11b*S*,12a*S*)-11a-Vinyl-7,8,11a,11b,12,12a-hexahydropyrrolizino[1′,7′:2,3,4]cyclopenta[1,2-*c*]quinoline-1,10(2*H*,11*H*)-dione (40)

Johnson–Claisen rearrangement of allylic alcohol 32 with trimethylorthoacetate (39): Allylic alcohol **32** (5.00 g, 13.5 mmol) and hydroquinone (1.00 g, 20 wt%, 9.08 mmol, 0.67 equiv) in trimethylorthoacetate (20.0 mL, 18.9 g, 157 mmol, 12 equiv) were heated to 130 °C for 4.0 h. The mixture was concentrated to about 4 mL in vacuum yielding a thick orange oil, which was stirred at 130 °C for an additional 16 h. After evaporation to dryness, the residue was purified by flash chromatography (5.0×25 cm, P/EtOAc 2:1→1:2) to give rearrangement product **39** (4.87 g, 11.4 mmol, 85%) as an inseparable mixture of diastereoisomers (d.r. 70:30) which was used directly in the next step. $R_f = 0.36$ (P/EtOAc 1:2, [UV]); MS (ESI): m/z: 449 [$M+Na^+$], 659 [$(3M+H^++K^+)/2^+$], 875 [$2M+Na^+$], 1005 [$2M+HCOOH+HCOONa+Na^+$], 1141 [$2M+2HCOOH+HCOONa+HCOOK+K^+$]; HPLC (ODS-A, MeCN/$H_2O$ 20:80→100:0, 30 min): $t_R = 18.7$ min (*N-cis*-vinyl, major), $t_R = 19.3$ min (*N-trans*-vinyl, minor).

N-Boc deprotection and N-alkylation of rearragement product 39: Rearrangement product **39** (560 mg, 1.31 mmol, d.r. 70:30) was stirred in 15 vol% TFA in CH_2Cl_2 (20 mL) for 1.0 h and evaporated to dryness. The residue was dissolved in H_2O (30 mL) and the aqueous solution made basic with aqueous NaOH (2.0 M). The solution was extracted with CH_2Cl_2 (4×25 mL), adjusted to pH 8–9 with sat. aqueous NH_4Cl and extracted with CH_2Cl_2 (4×25 mL) again. The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The solid residue was dissolved in MeCN (15 mL), K_2CO_3 (181 mg, 1.31 mmol, 1.0 equiv) and allyl bromide (91 μL, 128 mg, 1.05 mmol, 0.8 equiv) were added and the solution stirred at RT for 20 h. H_2O (75 mL) was added and the mixture extracted with CH_2Cl_2 (4×50 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (3.5×20 cm, CH_2Cl_2/MeOH 50:1→20:1) to give allylamine **42** (312 mg, 851 μmol, 65%, 93% rel. to d.r.) as the unpolar and pentacyclic lactam **40** (110 mg, 374 μmol, 29%, 95% rel. to d.r.) as the polar fraction as light yellow foams or solids. $R_f = 0.16$ (EtOAc, [UV]); m.p. 195–202 °C (decomp); ^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 9.82$ (br s, 1H, NH), 7.32 (d, $^3J = 7.3$ Hz, 1H, H_8), 7.23 (t, $^3J = 7.6$ Hz, 1H, H_6), 7.10 (t, $^3J = 7.6$ Hz, 1H, H_7), 6.91 (d, $^3J = 7.9$ Hz, 1H, H_5), 5.77 (dd, $^3J_E = 17.4$, $^3J_Z = 10.7$ Hz, 1H, =CH), 4.93 (d, $^3J = 10.7$ Hz, =CHH_E), 4.91 (d, $^3J = 17.4$ Hz, 1H, =CH_ZH), 4.48 (s, 1H, CHN), 3.97 (ddd, $^2J = 12.1$, $^3J = 8.1$, $^3J = 7.5$ Hz, 1H, CH*H*N), 3.29 (ddd, $^3J = 12.1$, $^3J = 9.9$, $^3J = 3.0$ Hz, 1H, C*H*HN), 3.08 (d, $^2J = 17.3$ Hz, 1H, CH*H*CON), 2.76 (virt. t, $^3J = 9.9$ Hz, 1H, C_{2a}H), 2.49 (d, $^2J = 17.3$ Hz, 1H, C*H*HCON), 2.51–2.43 (m, 1H, RCH*H*), 2.28–2.20 (m, 2H, C_2HH), 2.13 ppm (ddd, $^2J = 13.6$, $^3J = 9.9$, $^3J = 7.5$ Hz, 1H, RC*H*H); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 175.7$ (s, $CONR_2$), 171.0 (s, CONH), 141.9 (d, =CH), 135.9 (s, C_{4a}), 128.5 (d, C_6H), 126.2 (d, C_8H), 124.2 (d, C_7H), 122.8 (s, C_{8a}), 116.3 (d, C_5H), 113.5 (t, $=CH_2$), 81.8 (d, CHN), 55.3 (s, C_{8b}), 49.4 (s, C_1), 48.1 (d, C_{2a}H), 45.95 (t, CH_2CON/C_2HH), 45.88 (t, CH_2CON/C_2HH), 42.5 (t, CH_2N), 40.6 ppm (t, RCH_2); IR (ATR, neat): $\tilde{\nu} = 3211$ (w, NH), 3079/3063 (w, $C_{ar/olef}$H), 2966/2928 (w, C_{al}H), 1670 (vs, br., CON), 1592 (s, C_{ar}), 1487 (s), 1364 (s, br.), 1241 (m), 917 (m), 756 (m, C_{ar}), 726 cm^{-1} (m, C_{ar}); MS (70 eV): m/z (%): 294 (100) [M^+], 172 (51), 123 (26); MS (ESI): m/z: 295 [$M+H^+$], 611 [$2M+Na^+$], 905 [$3M+Na^+$]; HRMS (70 eV): m/z: calcd for $C_{18}H_{18}N_2O_2$: 294.1368 [M^+], found 294.1371.

Enantiopure: According to the above sequence consisting of Johnson–Claisen rearrangement and *N*-Boc deprotection followed by lactamization enantiomerically pure pentacyclic lactam (−)-**40** (43 mg, 176 μmol, 31%, quant. rel. to d.r.) was obtained with >99% *ee* when starting from the enantiomerically pure allylic alcohol (+)-**32**. $[\alpha]_D^{20} = -18.2$ ($c = 1.0$ in CH_2Cl_2); chiral HPLC (Chiralpak AD-H, *n*-hexane/*i*PrOH 80:20): $t_R = 28.6$ min, $k = 7.5$; *rac*: $t_R = 27.3/29.4$ min, $k = 7.0/7.6$, $\alpha = 1.09$.

(−)-(1*S*,2a*S*,8b*R*,11a*S*)-2-[11-Allyl-3-oxo-1-vinyl-2,2a,3,4,9,10,11,11a-octahydro-1*H*-pyrrolo[3′,2′:2,3]cyclopenta[1,2-c]quinoline-1-yl]methylacetate (42): $R_f = 0.55$ (EtOAc, [UV]); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.60$ (br s, 1H, NH), 7.30 (d, $^3J = 7.5$ Hz, 1H, H_8), 7.17 (t, $^3J = 7.5$ Hz, 1H, H_6), 7.07 (t, $^3J = 7.6$ Hz, 1H, H_7), 6.78 (d, $^3J = 7.9$ Hz, 1H, H_5), 6.27 (dd, $^3J_E = 17.9$, $^3J_Z = 10.9$ Hz, 1H, $=CH_{Vin}$), 5.94 (dddd, $^3J_E = 16.9$, $^3J_Z = 10.2$, $^3J = 6.6$, $^3J = 5.9$ Hz, 1H, $=CH_{All}$), 5.26 (dd, $^3J = 16.9$, $^{2/4}J = 1.1$ Hz, 1H, $=CHH_{All}$), 5.20–5.11 (m, 3H, $=CHH_{All}$, $=CH_{2\,Vin}$), 3.56 (s, 1H, CHN), 3.57–3.47 (m, 1H, NCHH), 3.48 (s, 3H, OCH_3), 3.22–3.12 (m, 2H, NCHH, CHHN), 2.94 (dd, $^3J = 10.6$, $^3J = 6.1$ Hz, 1H, C_{2a}H), 2.83 (virt. dt, $^2J = 10.8$, $^3J = 6.7$ Hz, 1H, CHHN), 2.53 (dd, $^2J = 13.8$, $^3J = 6.1$ Hz, 1H, CHH_{exo}), 2.49 (d, $^2J = 14.2$ Hz, 1H, CHHCOO), 2.30 (d, $^2J = 14.2$ Hz, 1H, CHHCOO), 2.04 (dd, $^2J = 13.8$, $^3J = 10.6$ Hz, 1H, CH_{endo}H), 1.96 (virt. dt, $^2J = 12.8$, $^3J = 6.7$ Hz, 1H, RCHH), 1.81 ppm (virt. dt, $^2J = 12.8$, $^3J = 6.7$ Hz, 1H, RCHH); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 171.7$ (s, CO), 171.5 (s, CO), 140.3 (d, $=CH_{Vin}$), 136.2 (d, $=CH_{All}$), 134.8 (s, C_{4a}), 129.1 (s, C_{8a}), 127.6 (d, C_8H), 127.5 (d, C_6H), 123.9 (d, C_7H), 117.0 (t, $=CH_{2\,All}$), 115.7 (d, C_5H), 112.2 (t, $=CH_{2\,Vin}$), 87.2 (d, CHN), 58.8 (t, NCH_2), 57.9 (s, C_{8b}), 54.8 (t, CH_2N), 51.2 (q, OCH_3), 49.5 (d, C_{2a}H), 48.3 (s, C_1), 44.5 (t, CH_2COO), 42.1 (t, C_2HH), 41.6 ppm (t, RCH_2); IR (ATR, neat): $\tilde{\nu} = 3200$ (w, NH), 3074 (w, $C_{ar/olef}$H), 2949 (m, C_{al}H), 1734 (s, COOEt), 1671 (vs, CONH),

1591 (s, C_{ar}), 1488 (s), 1110 (m, br.), 915 (s), 753 cm^{-1} (s, C_{ar}); MS (70 eV): *m/z* (%): 366 (8) [M^+], 335 (10) [$M-OMe^+$], 307 (7) [$M-COOMe^+$], 293 (10) [$M-CH_2COOMe^+$], 240 (50), 239 (81), 199 (100) [$C_{13}H_{16}N_2O^+$], 167 (15), 149 (20), 57 (14) [tBu^+], 41 (21) [$C_3H_5^+$]; HRMS (70 eV): *m/z*: calcd for $C_{22}H_{26}N_2O_3$: 366.1943 [M^+], found 366.1940; elemental analysis calcd (%) for $C_{22}H_{26}N_2O_3$: C 72.11, H 7.15; found: C 71.99, H 7.09.

Enantiopure: According to the above sequence consisting of Johnson–Claisen rearrangement and *N*-alkylation, enantiomerically pure allylamine (−)-**42** was obtained with >99% *ee* when starting from the enantiomerically pure allylic alcohol (+)-**32**. $[\alpha]_D^{20}=-36.2$ ($c=1.0$ in CH_2Cl_2); chiral HPLC (Chiralpak AD-H, *n*-hexane/*i*PrOH 90:10): $t_R=18.2$ min, $k=4.5$; rac: $t_R=15.6/19.6$ min, $k=3.5/4.6$, $\alpha=1.3$.

(+)-(6b*R*,12a*S*,12b*S*,13a*S*)-2-[1-Oxo-1,2,7,8,13,13a-hexahydro-10*H*-indolizino[1′,8′:2,3,4]cyclopenta[1,2-*c*]quinoline-12(12b*H*)-yl]methylacetate (44): Allylamine **42** (2.15 g, 5.87 mmol) and second generation Grubbs catalyst (249 mg, 294 μmol, 5 mol%) in PhMe (1.47 L) were heated to 60°C. After 2.5 h, a second load of Grubbs catalyst (249 mg, 294 μmol, 5 mol%) was added and the solution stirred at 60°C for 6.0 h. After evaporation of the solvent, the residue was purified by flash chromatography (5.0×20 cm CH_2Cl_2/MeOH 40:1→20:1) to give recovered starting material **42** (264 mg, 720 μmol, 12%) as the unpolar, and melodan ester **44** (1.65 g, 4.88 mmol, 83%, 95% b.r.s.m.) as the polar fraction as brown to violet oils. Attempts to remove colored Ru contaminants by chromatography were ineffective. Ester **44** could however be converted to the equal amount of a light brown solid by precipitation with Et_2O (200 mL). $R_f=0.50$ (CH_2Cl_2/MeOH 10:1, [UV]); ^{1}H NMR (360 MHz, $CDCl_3$): $\delta=$ 9.62 (br s, 1H, NH), 7.39 (d, $^3J=7.5$ Hz, 1H, H_{14}), 7.15 (t, $^3J=7.2$ Hz, 1H, H_{16}), 7.05 (t, $^3J=7.4$ Hz, 1H, H_{15}), 6.84 (d, $^3J=7.7$ Hz, 1H, H_{17}), 5.95 (ddd, $^3J_Z=9.8$, $^3J=5.3$, $^3J=1.6$ Hz, 1H, CH_2CH=), 5.86 (dd, $^3J_Z=9.8$, $^4J=$ 1.9 Hz, 1H, =CHC), 3.58 (s, 1H, CHN), 3.50 (s, 3H, OCH_3), 3.26 (dd, $^2J=16.3$, $^3J=5.3$ Hz, 1H, NCH*H*), 3.21–3.08 (m, 2H, NC*H*H, CH*H*N), 3.01 (dd, $^3J=10.3$, $^3J=8.6$ Hz, 1H, C_3H), 2.86 (virt. dt, $J_t=8.3$, $J_d=$ 4.8 Hz, 1H, C*H*HN), 2.43 (dd, $^2J=13.0$, $^3J=8.6$ Hz, 1H, CH_{exo}), 2.25–2.10 (m, 3H, CH_2COO, RCH*H*), 2.03 (dd, $^2J=13.0$, $^3J=10.3$ Hz, 1H, CH_{endo}H), 1.89 ppm (virt. dt, $^2J=13.0$, $^3J=7.3$ Hz, 1H, RC*H*H); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta=172.6$ (s, CONH), 171.3 (s, COOMe), 135.4 (s, C_{18}), 132.4 (d, =*C*HC), 127.7 (d, C_{16}H), 127.5 (d, C_{14}H), 127.1 (d, CH_2CH=), 126.9 (s, C_{13}), 123.9 (d, C_{15}H), 115.8 (d, C_{17}H), 80.0 (d, CHN), 56.9 (s, C_{12}), 52.7 (t, CH_2N), 51.2 (q, OCH_3), 50.4 (d, C_3H), 46.7 (t, NCH_2), 44.6 (t, CH_2COO), 44.3 (t, C_4HH), 43.2 (s, C_5), 40.9 ppm (t, RCH_2); IR (ATR, neat): $\tilde{\nu}=$3194 (w, NH), 3059 (w, $C_{ar/olef}$H), 2958 (m, C_{al}H), 2929 (m, C_{al}H), 1727 (s, COOMe), 1671 (vs, CONH), 1594 (m, C_{ar}), 1494 (s), 1432 (m), 1391 (s), 1163 (m), 1113 (m), 770 cm^{-1} (m, C_{ar}); MS (70 eV): *m/z* (%): 338 (100) [M^+], 323 (5) [$M-Me^+$], 307 (13) [$M-OMe^+$], 279 (19) [$M-COOMe^+$], 265 (56) [$M-CH_2COOMe^+$], 264 (49), 214 (43), 205 (42), 180 (27), 132 (27), 91 (28) [$C_7H_7^+$], 57 (24) [tBu^+], 43 (15) [$C_3H_5^+$]; HRMS (70 eV): *m/z*: calcd for $C_{20}H_{22}N_2O_3$: 338.1631 [M^+], found 338.1621.

Enantiopure: According to the above procedure, enantiomerically pure melodan ester (+)-**44** was obtained with >99% *ee* when starting from the enantiomerically pure allyl amine (−)-**42**. $[\alpha]_D^{20}=+147$ ($c=0.1$ in CH_2Cl_2); chiral HPLC (Chiralpak AD-H, *n*-hexane/*i*PrOH 80:20): $t_R=$ 12.1 min, $k=2.5$; *rac*: $t_R=13.6/15.2$ min, $k=2.3/2.7$, $\alpha=1.17$.

(±)-(6b*R*,12a*S*,12b*S*,13a*S*)-2-[1-Oxo-1,2,7,8,13,13a-hexahydro-10*H*-indolizino[1′,8′:2,3,4]cyclopenta[1,2-*c*]quinoline-12(12b*H*)-yl]acetaldehyde (45): Melodan ester **44** (41 mg, 121 μmol) was dissolved in dry CH_2Cl_2 (10 mL) and cooled to −70°C. DIBAL-H (1.1 M in cyclohexane, 260 μL, 286 μmol, 2.4 equiv) was added and the solution stirred for 2.0 h at −70°C. The reaction was quenched with a few drops of MeOH and the solvent evaporated. Purification of the solid residue by flash chromatography (2.5×10 cm, CH_2Cl_2/MeOH 15:1→10:1) gave melodan aldehyde **45** (28 mg, 91 μmol, 75%) as a white foam. $R_f=0.46$ (CH_2Cl_2/MeOH 8:2, [UV]); ^{1}H NMR (360 MHz, $CDCl_3$): $\delta=9.55$ (t, $^3J=2.1$ Hz, 1H, CHO), 9.15 (br s, 1H, NH), 7.42 (d, $^3J=7.7$ Hz, 1H, H_{14}), 7.18 (t, $^3J=7.6$ Hz, 1H, H_{16}), 7.07 (t, $^3J=7.5$ Hz, 1H, H_{15}), 6.82 (d, $^3J=7.9$ Hz, 1H, H_{17}), 5.98 (ddd, $^3J_Z=9.9$, $^3J=5.4$, $^3J=1.8$ Hz, 1H, CH_2CH=), 5.89 (dd, $^3J_Z=9.9$, $^4J=$ 2.0 Hz, 1H, =CHC), 3.49 (br s, 1H, CHN), 3.35 (dd, $^2J=16.6$, $^3J=5.4$ Hz, 1H, NCH*H*), 3.25–3.13 (m, 2H, NC*H*H, CH*H*N), 3.06 (virt. t, $^3J=9.4$ Hz, 1H, C_3H), 2.94 (br virt. dt, $J_t=7.9$, $J_d=5.3$ Hz, 1H, C*H*HN), 2.52 (dd, $^2J=13.2$, $^3J=8.6$ Hz, 1H, CHH_{exo}), 2.28 (d, $^3J=2.1$ Hz, 2H, CH_2CHO), 2.19 (ddd, $^2J=13.0$, $^3J=7.0$, $^3J=5.2$ Hz, 1H, RCH*H*), 2.02–1.91 ppm (m, 2H, CH_{endo}H, RC*H*H); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta=200.9$ (d, CHO), 171.9 (s, CONH), 135.2 (s, C_{18}), 132.3 (d, =*C*HC), 128.0 (d, C_{16}H), 127.5 (d, C_{14}H), 126.7 (d, CH_2CH=), 126.4 (s, C_{13}), 124.3 (d, C_{15}H), 115.8 (d, C_{17}H), 80.2 (d, CHN), 57.0 (s, C_{12}), 53.4 (t, CH_2CHO), 52.8 (t, CH_2N), 50.6 (d, C_3H), 46.9 (t, NCH_2), 44.7 (t, C_4HH), 43.1 (s, C_5), 40.8 ppm (t, RCH_2); IR (ATR, neat): $\tilde{\nu}=$3186 (w, NH), 3055 (w, $C_{ar/olef}$H), 2924 (m, C_{al}H), 1717 (s, CHO), 1668 (vs, CONH), 1593 (s, C_{ar}), 1492 (s), 1389 (s), 1250 (m), 756 (m, C_{ar}), 727 cm^{-1} (w); MS (70 eV): *m/z* (%): 308 (16) [M^+], 279 (13) [$M-CHO^+$], 264 (100) [$M-CH_2CH_2O^+$], 235 (12), 84 (44), 59 (23), 41 (12); HRMS (70 eV): *m/z*: calcd for $C_{19}H_{20}N_2O_2$: 308.1525 [M^+], found 308.1517.

(+)-(6b*R*,12a*S*,12b*S*,13a*S*)-12a-(2-Hydroxyethyl)-7,8,12a,12b,13,13a-hexahydro-10*H*-indolizino[1′,8′:2,3,4]cyclopenta[1,2-*c*]quinolin-1(2*H*)-one (46): Melodan ester **44** (200 mg, 591 μmol) was dissolved in dry CH_2Cl_2 (50 mL) and cooled to −70°C. DIBAL-H (1.1 M in cyclohexane, 1.13 mL, 1.24 mmol, 2.1 equiv) was added slowly and the solution stirred for 1.5 h at −70°C. The reaction was quenched with MeOH (5 mL) and the solvent evaporated. The solid residue was suspended in dry EtOH (50 mL) and cooled to 0°C. Fresh $NaBH_4$ (26.8 mg, 709 μmol, 1.2 equiv) was added and the mixture stirred at 0°C for 25 min. The reaction was quenched with aqueous HCl (10%, 5 mL) and the solvent removed in vacuum. The residue was dissolved in H_2O (30 mL) and CH_2Cl_2 (30 mL), the solution made basic with aqueous NaOH (2 M), phases were separated and the aqueous phase was extracted with CH_2Cl_2 (5×30 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated to give melodan alcohol **46** (172 mg, 554 μmol, 94%) as a slightly gray foam of sufficient purity (ca. 90% NMR). Attempted additional purification by flash chromatography was ineffective due to the very high polarity of the product alcohol. $R_f=0.28$ (CH_2Cl_2/MeOH 8:2, [UV]); ^{1}H NMR (500 MHz, $CDCl_3$; $c\approx 10$ mg mL^{-1}): $\delta=8.47$ (br s, 1H, NH), 7.41 (br d, $^3J=7.0$ Hz, 1H, H_{14}), 7.16 (dt, $^3J=7.6$, $^4J=1.4$ Hz, 1H, H_{16}), 7.06 (dt, $^3J=7.5$, $^4J=1.2$ Hz, 1H, H_{15}), 6.74 (dd, $^3J=7.9$, $^4J=1.4$ Hz, 1H, H_{17}), 5.96 (ddd, $^3J_Z=9.9$, $^3J=5.3$, $^3J=2.3$ Hz, 1H, CH_2CH=), 5.77 (dt, $^3J_Z=9.9$, $^4J=1.9$ Hz, 1H, =CHC), 3.60–3.47 (m, 3H, CHN, CH_2OH), 3.26 (dd, $^2J=16.2$, $^3J=5.3$ Hz, 1H, NCH*H*), 3.21–3.13 (m, 2H, NC*H*H, CH*H*N), 2.92 (dd, $^3J=10.1$, $^3J=8.3$ Hz, 1H, C_3H), 2.88 (ddd, $^2J=8.8$, $^3J=$ 8.2, $^3J=4.8$ Hz, 1H, C*H*HN), 2.29 (dd, $^2J=12.7$, $^3J=8.3$ Hz, 1H, CHH_{exo}), 2.12 (ddd, $^2J=12.8$, $^3J=6.6$, $^3J=4.8$ Hz, 1H, RCH*H*), 1.96–1.88 (m, 2H, RC*H*H, CH_{endo}H), 1.51 ppm (virt. dt, $^3J_t=7.0$, $J_d=3.3$ Hz, 2H, CCH_2); the ^{1}H NMR spectrum is very strongly dependent on the concentration, giving a distinctly different set of signals at $c\approx 50$ mg mL^{-1} due to intra- and intermolecular hydrogen bonding; ^{13}C NMR (90 MHz, $CDCl_3$): $\delta=171.7$ (s, CONH), 135.0 (s, C_{18}), 133.7 (d, =*C*HC), 127.8 (d, C_{16}H), 127.7 (d, C_{14}H), 127.3 (s, C_{13}), 126.4 (d, CH_2CH=), 124.2 (d, C_{15}H), 115.5 (d, C_{17}H), 80.3 (d, CHN), 59.9 (t, CH_2OH), 57.1 (s, C_{12}), 53.1 (t, CH_2N), 50.2 (d, C_3H), 46.5 (t, NCH_2), 45.1 (t, C_4HH), 43.7 (s, C_5), 43.6 (t, CCH_2), 41.1 (t, RCH_2); IR (ATR, neat): $\tilde{\nu}=$3350 (m, vbr, OH), 3213 (w, NH), 3061 (w, $C_{ar/olef}$H), 2926 (m, C_{al}H), 1665 (vs, CONH), 1592 (s, C_{ar}), 1488 (m), 1383 (s), 1242 (m), 1046 (m), 755 cm^{-1} (s, C_{ar}); MS (70 eV): *m/z* (%): 310 (100) [M^+], 296 (17), 279 (33) [$M-CH_2OH^+$], 266 (52), 172 (32), 154 (61), 152 (52), 108 (33), 45 (23) [$CH_2CH_2OH^+$]; HRMS (70 eV): *m/z*: calcd for $C_{19}H_{22}N_2O_2$: 310.1681 [M^+], found 310.1670.

Enantiopure: According to the above procedure, enantiomerically pure melodan alcohol (+)-**46** (98 mg, 316 μmol, 58% after chromatography) was obtained with >99% *ee* when starting from the enantiomerically pure melodan ester (+)-**44**. $[\alpha]_D^{20}=+76$ ($c=0.1$ in CH_2Cl_2); chiral HPLC (Chiralpak AD-H, *n*-hexane/*i*PrOH 80:20): $t_R=12.0$ min, $k=2.5$; *rac*: $t_R=11.8/19.4$ min, $k=2.6/4.9$, $\alpha=1.9$.

(+)-(6b*R*,12a*S*,12b*S*,13a*S*)-12a-(2-Tosylethyl)-7,8,12a,12b,13,13a-hexahydro-10*H*-indolizino[1′,8′:2,3,4]cyclopenta[1,2-*c*]quinoline-1(2*H*)-one (47): Melodan alcohol **46** (115 mg, 370 μmol), NEt_3 (180 μL, 131 mg, 1.30 mmol, 3.5 equiv) and TosCl (177 mg, 926 μmol, 2.5 equiv) in CH_2Cl_2 (5.0 mL) were stirred for 18 h at RT. Sat. aqueous $NaHCO_3$ (50 mL) and CH_2Cl_2 (50 mL) were added, phases separated and the aqueous phase ex-

tracted with CH_2Cl_2 (2×25 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. Purification of the residue by flash chromatography (2.5×15 cm, CH_2Cl_2/MeOH 40:1→20:1) gave melodan tosylate **47** (123 mg, 265 μmol, 72%) as a light brown solid. In a three-step sequence with no purification of the intermediates, melodan ester **44** (338 mg, 1.00 mmol) could be converted into melodan tosylate **47** (243 mg, 523 μmol, 52%) while avoiding the difficulties of the isolation of the intermediate alcohol. R_f=0.45 (CH_2Cl_2/MeOH 10:1, [UV]); m.p. 175–178°C (MeOH); ^{1}H NMR (360 MHz, $CDCl_3$): δ=9.05 (brs, 1H, NH), 7.68 (d, ^3J=8.4 Hz, 2H, H_2), 7.37–2.28 (m, 3H, H_{14}, H_3), 7.15 (dt, ^3J=7.6, ^4J=1.3 Hz, 1H, H_{16}), 7.03 (dt, ^3J=7.5, ^4J=1.1 Hz, 1H, H_{15}), 6.79 (dd, ^3J=7.8, ^4J=1.0 Hz, 1H, H_{17}), 5.93 (ddd, ^3J_Z=9.9, ^3J=5.6, ^3J=2.0 Hz, 1H, CH_2CH=), 5.77 (dd, ^3J_Z=9.9, ^4J=2.0 Hz, 1H, =CHC), 3.97–3.85 (m, 2H, CH_2OTos), 3.36 (s, 1H, CHN), 3.24 (dd, ^2J=16.3, ^3J=5.6 Hz, 1H, NCH*H*), 3.13 (ddd, ^2J=8.6, ^3J=7.2, ^3J=6.8 Hz, 1H, CH*H*N), 3.03 (virt. dt, ^2J=16.3, ^3J=2.0 Hz, 1H, NC*H*H), 2.93 (dd, ^3J=10.2, ^3J=8.5 Hz, 1H, C_3H), 2.83 (ddd, ^2J=8.6, ^3J=7.9, ^3J=4.8 Hz, 1H, C*H*HN), 2.43 (s, 3H, $ArCH_3$), 2.28 (dd, ^2J=12.9, ^3J=8.5 Hz, 1H, CHH_{exo}), 2.11 (ddd, ^2J=12.7, ^3J=6.8, ^3J=4.8 Hz, 1H, RCH*H*), 1.86 (ddd, ^2J=12.7, ^3J=7.9, ^3J=7.2 Hz, 1H, RC*H*H), 1.79 (dd, ^2J=12.9, ^3J=10.2 Hz, 1H, CH_{endo}H), 1.65–1.45 ppm (m, 2H, CCH_2); ^{13}C NMR (90 MHz, $CDCl_3$): δ=172.1 (s, CONH), 144.7 (s, $C_{1'}$), 135.2 (s, C_{18}), 133.0 (s, $C_{4'}$), 132.7 (d, =*C*HC), 129.8 (d, C_3H), 127.83 (d, CH_2CH=), 127.79 (d, C_2H), 127.76 (d, C_{16}H), 127.4 (d, C_{14}H), 127.0 (s, C_{13}), 124.1 (d, C_{15}H), 115.7 (d, C_{17}H), 80.1 (d, CHN), 67.6 (t, CH_2OTos), 56.9 (s, C_{12}), 52.8 (t, CH_2N), 50.3 (d, C_3H), 46.8 (t, NCH_2), 45.0 (t, C_4HH), 43.5 (s, C_5), 41.1 (t, RCH_2), 39.4 (t, CCH_2), 21.6 ppm (q, $ArCH_3$); IR (ATR, neat): $\tilde{\nu}$=3203 (w, NH), 3060 (w, $C_{ar/olef}$H), 2921 (w, C_{al}H), 1669 (vs, CONH), 1593 (s, C_{ar}), 1489 (m), 1360 (s, OTos), 1174 (vs, OTos), 953 (m, br.), 813 (w), 754 cm^{-1} (s, C_{ar}); MS (70 eV): *m*/*z* (%): 464 (14) [M^+], 309 (100) [M−Tos$^+$], 292 (7) [M−TosOH$^+$], 265 (10), 172 (10), 134 (13), 120 (10), 91 (10) [$C_7H_7^+$]; HRMS (70 eV): *m*/*z*: calcd for $C_{26}H_{28}N_2O_4S$: 464.1770 [M^+], found 464.1797.

Enantiopure: According to the above procedure, enantiomerically pure melodan tosylate (+)-**47** was obtained with >99% *ee* when starting from the enantiomerically pure melodan alcohol (+)-**46** or melodan ester (+)-**44**. $[\alpha]_D^{20}$=+58.5 (*c*=1.0 in CH_2Cl_2); chiral HPLC (Chiralpak AD-H, *n*-hexane/*i*PrOH 80:20): t_R=30.7 min, *k*=8.0; *rac*: t_R=30.7/38.7 min, *k*=8.3/10.7, α=1.3.

(+)-(6b*R*,12a*S*,12b*S*,13a*S*)-12a-2-[(2-Nitrophenyl)selanyl]ethyl-7,8,12a,12b,13,13a-hexahydro-10*H*-indolizino[1′,8′:2,3,4]cyclopenta[1,2-*c*]quinoline-1(2*H*)-one (48): Melodan tosylate **47** (55 mg, 118 μmol) was dissolved in dry EtOH (5.0 mL) and treated with the deep red solution of selenid anion (5.8 equiv) prepared from 2-nitrophenylselenocyanate (166 mg, 731 μmol, 6.2 equiv) and $NaBH_4$ (25.9 mg, 684 μmol, 5.8 equiv $NaBH_4$) in dry EtOH (3.0 mL) at RT. After 3.5 h an additional 5.2 equiv of selenid anion were added and the solution stirred at RT for 18 h. Again, 5.4 equiv of selenid anion were added and after 4.0 h a final load of 5.4 equiv of selenid was added. The solution was stirred for an additional 32 h at RT during which time a light brown suspension was formed. Sat. aqueous $NaHCO_3$ (50 mL) was added and the mixture extracted with CH_2Cl_2 (4×40 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. Purification of the residue by flash chromatography (2.5×20 cm, CH_2Cl_2/MeOH 50:1→20:1) gave the melodan nitrophenylselenide **48** (57 mg, 115 μmol, 98%) as a brightly yellow foam containing no more than 5% (NMR) of the residual tosylate substrate. R_f=0.55 (CH_2Cl_2/MeOH 10:1, [UV]); ^{1}H NMR (360 MHz, $CDCl_3$): δ=9.36 (brs, 1H, NH), 8.22 (dd, ^3J=8.5, ^4J=1.2 Hz, 1H, $H_{3'}$), 7.42 (dt, ^3J=7.7, ^4J=1.3 Hz, 1H, $H_{5'}$), 7.40 (brd, ^3J=8.4 Hz, 1H, H_{14}), 7.33–7.23 (m, 2H, $H_{4'}$, $H_{6'}$), 7.15 (dt, ^3J=7.6, ^4J=1.3 Hz, 1H, H_{16}), 7.04 (dt, ^3J=7.6, ^4J=1.3 Hz, 1H, H_{15}), 6.81 (dd, ^3J=7.8, ^4J=1.0 Hz, 1H, H_{17}), 6.07 (ddd, ^3J_Z=9.9, ^3J=5.3, ^3J=1.9 Hz, 1H, CH_2CH=), 5.81 (dd, ^3J_Z=9.9, ^4J=2.0 Hz, 1H, =CHC), 3.49 (brs, 1H, CHN), 3.31 (dd, ^2J=16.8, ^3J=5.5 Hz, 1H, NCH*H*), 3.23–3.14 (m, 2H, NC*H*H, CH*H*N), 2.99 (dd, ^3J=9.4, ^3J=7.8 Hz, 1H, C_3H), 2.91 (ddd, ^2J=8.1, ^3J=8.1, ^3J=4.7 Hz, 1H, C*H*HN), 2.73 (dd, ^3J=9.4, ^3J=7.4 Hz, 2H, CH_2SeAr), 2.35 (dd, ^2J=12.8, ^3J=7.8 Hz, 1H, CHH_{exo}), 2.14 (ddd, ^2J=12.7, ^3J=6.6, ^3J=4.7 Hz, 1H, RCH*H*), 2.00–1.86 (m, 2H, RC*H*H, CH_{endo}H), 1.68–1.57 ppm (m, 2H, CCH_2); ^{13}C NMR (90 MHz, $CDCl_3$): δ=172.4 (s, CONH), 146.7 (s, $C_{2'}$), 135.2 (s, C_{18}), 133.5 (d, $C_{5'}$H), 133.3 (s, $C_{1'}$), 132.6 (d, =*C*HC), 128.7 (d, $C_{4'/6'}$H), 127.82 (d, CH_2CH=), 127.77 (d, C_{16}H), 127.3 (d, C_{14}H), 127.2 (s, C_{13}), 126.4 (d, $C_{3'}$H), 125.3 (d, $C_{4'/6'}$H), 124.0 (d, C_{15}H), 115.8 (d, C_{17}H), 79.9 (d, CHN), 57.0 (s, C_{12}), 53.0 (t, CH_2N), 50.3 (d, C_3H), 47.0 (t, NCH_2), 45.8 (s, C_5), 44.5 (t, C_3HH), 41.4 (t, RCH_2), 39.5 (t, CCH_2), 21.3 ppm (t, CH_2SeAr); IR (ATR, neat): $\tilde{\nu}$=3194 (w, NH), 3052 (w, $C_{ar/olef}$H), 2925 (w, C_{al}H), 1668 (vs, CONH), 1591 (s), 1508 (vs, NO_2), 1330 (s, NO_2), 1038 (m), 848 (m, NO_2), 756 (s, C_{ar}), 724/700/670 cm^{-1} (s, $ArNO_2$); MS (70 eV): *m*/*z* (%): 495 (23) [M(^{80}Se)$^+$], 493 (14) [M(^{78}Se)$^+$], 478 (82) [M(^{80}Se)−OH$^+$], 476 (39) [M(^{78}Se)−OH$^+$], 373 (40) [M(^{80}Se)−Ar$^+$], 371 (19) [M(^{78}Se)−Ar$^+$], 328 (36), 309 (100), 265 (56), 106 (28), 59 (43) [*t*Bu$^+$], 41 (17) [$C_3H_7^+$]; HRMS (70 eV): *m*/*z*: calcd for $C_{25}H_{25}N_3O_3Se$: 495.1061 [M^+], found 495.1051.

Enantiopure: According to the above procedure, enantiomerically pure melodan selenide (+)-**48** was obtained with >99% *ee* when starting from the enantiomerically pure melodan tosylate (+)-**47**. $[\alpha]_D^{20}$=+167 (*c*=0.1 in CH_2Cl_2); chiral HPLC (Chiralpak AD-H, *n*-hexane/*i*PrOH 80:20): t_R=11.2 min, *k*=2.4; *rac*: t_R=12.3/18.7 min, *k*=2.7/4.7, α=1.74.

(+)-(6b*R*,12a*S*,12b*S*,13a*S*)-12a-Vinyl-7,8,12a,12b,13,13a-hexahydro-10*H*-indolizino[1′,8′:2,3,4]cyclopenta[1,2-*c*]quinoline-1(2*H*)-one, (+)-meloscine (1): Melodan selenide **48** (45 mg, 91 μmol) was dissolved in CH_2Cl_2 (10 mL), TFA (10.2 μL, 15.6 mg, 137 μmol, 1.5 equiv) was added and the solution cooled to −78°C. A solution of MCPBA (20.5 mg, 77% aq., 15.8 mg, 91 μmol, 1.00 equiv) in CH_2Cl_2 (3.0 mL) was added and the mixture stirred for 1.5 h at −78°C. The reaction was quenched with Me_2S (0.32 mL, 283 mg, 4.55 mmol, 50 equiv) and NEt_3 (0.38 mL, 276 mg, 2.73 mmol, 30 equiv) and the reaction mixture warmed to RT, at which it was stirred for an additional 2.0 h. Sat. aqueous $NaHCO_3$ (20 mL) and CH_2Cl_2 (20 mL) were added, phases separated and the aqueous phase extracted with CH_2Cl_2 (3×25 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. Purification of the crude product by flash chromatography (1.0×15 cm, CH_2Cl_2/MeOH 50:1→20:1) gave (±)-meloscine (**1**) (23.0 mg, 78.7 μmol, 86%) as an off-white solid. R_f=0.33 (CH_2Cl_2/MeOH 10:1, [UV]); m.p. 216–220°C (Et_2O/MeOH); ^{1}H NMR (360 MHz, $CDCl_3$): δ=9.18 (brs, 1H, NH), 7.38 (brd, ^3J=7.5 Hz, 1H, H_{14}), 7.14 (td, ^3J=7.6, ^4J=1.3 Hz, 1H, H_{16}), 7.04 (td, ^3J=7.5, ^4J=1.4 Hz, 1H, H_{15}), 6.79 (dd, ^3J=7.8, ^4J=1.0 Hz, 1H, H_{17}), 6.01 (ddd, ^3J_Z=9.8, ^3J=5.6, ^3J=2.2 Hz, 1H, NCH_2CH=), 5.73 (dd, ^3J_Z=9.8, ^4J=2.2 Hz, 1H, =CHC_5), 5.54 (dd, ^3J_E=17.3, ^3J_Z=10.6 Hz, 1H, *CH*=CH_2), 4.90 (dd, ^3J_E=17.3, ^2J=0.5 Hz, 1H, =CH$H_{pro\text{-}Z}$), 4.78 (dd, ^3J_Z=10.6, ^2J=0.5 Hz, 1H, =C*H*$H_{pro\text{-}E}$), 3.55 (brs, 1H, CHN), 3.30 (dd, ^2J=15.1, ^3J=5.6 Hz, 1H, NCHH_i), 3.20 (ddd, ^2J=8.3, ^3J=7.7, ^3J=7.1 Hz, 1H, CH_iH$_a$N), 3.15 (ddd, ^2J=15.1, ^3J=2.2, ^4J=2.2 Hz, 1H, NCH_aH), 2.95 (dd, ^3J=9.6, ^3J=8.3 Hz, 1H, C_3H), 2.89 (ddd, ^2J=8.3, ^3J=7.8, ^3J=4.5 Hz, 1H, CH_aHN), 2.31 (dd, ^2J=12.7, ^3J=8.3 Hz, 1H, CHH_{exo}), 2.17 (dd, ^2J=12.7, ^3J=9.6 Hz, 1H, CH_{endo}H), 2.11 (ddd, ^2J=12.8, ^3J=7.1, ^3J=4.5 Hz, 1H, RCHH_i), 1.95 ppm (ddd, ^2J=12.8, ^3J=7.8, ^3J=4.5 Hz, 1H, RCH_aH); ^{13}C NMR (90 MHz, $CDCl_3$): δ=172.4 (s, CONH), 143.2 (d, *CH*=CH_2), 135.2 (s, C_{18}), 132.5 (d, =*C*HC_5), 127.7 (d, C_{14}H), 127.6 (d, C_{16}H), 127.5 (s, C_{13}), 127.0 (d, CH=), 123.9 (d, C_{15}H), 115.5 (d, C_{17}H), 112.6 (t, CH=*C*H_2), 82.3 (d, CHN), 56.9 (s, C_{12}), 53.0 (t, CH_2N), 50.8 (d, C_3H), 48.0 (s, C_5), 46.7 (t, N*C*H_2CH=), 43.4 (t, C_2HH), 42.0 ppm (t, RCH_2); IR (ATR, neat): $\tilde{\nu}$=3188 (w, CONH), 3054 (w, $C_{ar/olef}$H), 2982 (m, C_{al}H), 2926 (m, CH_2), 2770 (m), 1656 (vs, CONH), 1593 (s), 1501 (m), 1397 (s), 1253 (m), 930 (m), 871 (m), 755 (s, C_{ar}), 679 cm^{-1} (m, C_{olef}); UV/Vis (EtOH): λ_{max} (ε)=253 (10000), shoulders at 280 (2000), 290 nm (1600), λ_{min} (ε)=230 nm (5250 mol^{-1} m^{3}cm^{-1}); MS (70 eV): *m*/*z* (%): 292 (100) [M^+], 277 (17), 264 (26) [M−$C_2H_4^+$], 210 (23), 172 (24) [$C_{11}H_{10}NO^+$], 159 (17) [$C_{10}H_9NO^+$], 134 (74) [$C_9H_{12}N^+$], 120 (24) [$C_8H_{10}N^+$], 91 (21) [$C_7H_7^+$], 77 (26) [$C_6H_5^+$], 57 (14) [*t*Bu$^+$], 41 (21) [$C_3H_5^+$]; HRMS (70 eV): *m*/*z*: calcd for $C_{19}H_{20}N_2O$: 292.1576 [M^+], found 292.1574.

Enantiopure: According to the above procedure, enantiomerically pure meloscine (+)-**1** was obtained with >99% *ee* when starting from the enantiomerically pure melodan selenide (+)-**48**. m.p. 172–176°C (Et_2O); $[\alpha]_D^{20}$=+90.6 (*c*=0.5 in CH_2Cl_2); chiral HPLC (Chiralpak AD-H, *n*-hexane/*i*PrOH 95:5, *T*=5°C): t_R=24.0 min, *k*=6.1; *rac*: t_R=26.8/31.5 min, *k*=6.9/8.3, α=1.2.

Acknowledgements

Our research was supported by the Deutsche Forschungsgemeinschaft (Schwerpunktprogramm 1179 Organokatalyse), by the Fonds der Chemischen Industrie and by the Studienstiftung des Deutschen Volkes (PhD-scholarship to P.S.). The help of Mr. Olaf Ackermann in obtaining chiral HPLC data is gratefully acknowledged.

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Received: November 17, 2008
Published online: February 13, 2009

