Total Synthesis

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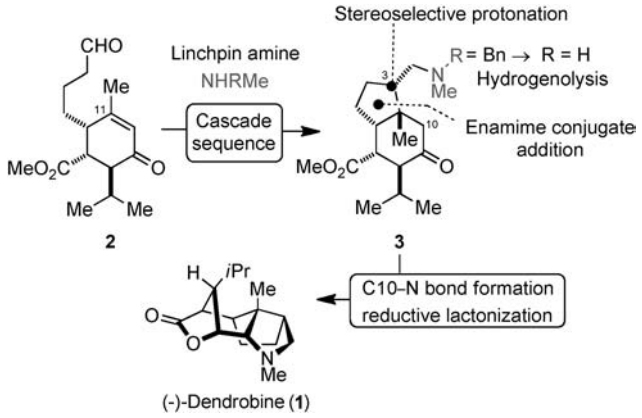
Total Synthesis of (−)-Dendrobine**

*Lukas M. Kreis and Erick M. Carreira**

(−)-Dendrobine (**1**) is the most abundant alkaloid isolated from the ornamental orchid *Dendrobium nobile* Lindl.[1] Extracts of this orchid are used in Chinese medicine as a tonic and exhibit antipyretic, hypertensive, and convulsant activity.[2] The intriguing structure of (−)-dendrobine (**1**), which includes a tetracyclic ring system with seven contiguous stereocenters, has been the object of intensive studies by the synthetic community.[3–7] Herein, we present an efficient route for the asymmetric total synthesis of (−)-dendrobine (**1**; Scheme 1). The strategy is based on a key reaction cascade



Scheme 1. Strategy for the construction of the core of (−)-dendrobine (**1**). Bn = benzyl.

with an amine functioning as the linchpin, wherein it initiates the sequence of reactions and embeds itself in the target structure. Interestingly, the overall transformation occurs stereoselectively only when the conversion of **2** to **3** is carried out without the isolation of intermediates, thus providing an efficient means of installing both the quaternary center at C11 and the stereocenter at C3 (Scheme 1).

Much like the erythronolides for polyketides,[8] dendrobine has served as a target to examine novel tactics and strategies for chemical synthesis. Of the various syntheses that have been reported,[3–6] only two provide access to enantiopure material, with yields for the longest linear sequences of 1.7 %[5a] and 1.3 %.[5b] Three formal enantioselective syntheses have been reported with yields ranging from 0.2–2.0 %.[6] In our analysis of the target, we viewed the synthesis of the core as an opportunity to study and implement a cascading sequence of reactions (Scheme 1, **2**→**3**) in which an amine condenses with an aldehyde to give an enamine that initiates cyclization onto an enone, followed by a reduction/deprotection sequence. Although the use of enamines and Michael acceptors has received great attention recently in the form of new methods involving organocatalysis,[9–13] absent altogether from this literature is conjugate addition to β-substituted enones to generate quaternary centers.

The synthesis we delineate herein commences with enantiomerically pure ester **4**, prepared in two steps and 76 % yield[14] from commercially available starting materials (Scheme 2). It is converted into **5** through a six-step sequence, which proceeds in 60 % overall yield. Vinyl lithium **6**[15] undergoes addition to aldehyde **5** at 0 °C to furnish product **7** as a 2.2:1 mixture of diastereomeric allylic alcohols.[16,17] Deprotection of the benzoate ester in the adduct employing standard alkaline conditions resulted in scrambling of the silyl protecting group. Subsequent experimentation revealed that the action of EtMgBr led to smooth removal of the benzoate group.[18] This step was implemented in the same pot following the aldehyde addition, to furnish a mixture of separable diastereomeric diols. Diol **7** was then transformed into lactone **8** in 88 % yield following the protocol of Forsyth and coworkers,[19] employing TEMPO and diacetoxyiodobenzene. Lactonic Ireland–Claisen rearrangement proceeded smoothly and afforded **9** after esterification in 95 % yield over two steps. This strategy provides efficient access to the highly substituted cyclohexane core of (−)-dendrobine (**1**).[20]

Unexpected difficulties were met in attempts to remove the silyl groups in **9**. The use of Bu_4NF led to formation of the corresponding butyrolactone, and acidic conditions triggered elimination. However, HF·pyridine proved to be sufficiently mild for this delicate deprotection. Both liberated primary and secondary alcohols were then oxidized with PCC,[21] and the key intermediate **10** was isolated in 67 % yield from **9**. With **10** in hand, we were then able to test the intramolecular enamine Michael addition sequence for installation of the quaternary center at C11. In the event, heating **10** in the presence of pyrrolidine furnished aldehyde **12** in 65 % yield, albeit as an inseparable 2:1 mixture of C3 diastereomeric aldehyde products.[22]

We next became interested in exploring ways in which to provide a more direct route to the core structure, with the expectation that it might also be possible to effect stereocontrol at C3. When **10** was treated with *N*-methylbenzylamine, cyclization was observed, and isolation of **12** once again furnished a mixture of stereoisomers at C3 (2:1). However, we then observed that coupling the amine-triggered cyclization to a subsequent reduction afforded **3** with high selectivity.

[*] L. M. Kreis, Prof. Dr. E. M. Carreira
Laboratorium für Organische Chemie, ETH Zürich, HCI H335
Wolfgang-Pauli-Strasse 10, 8093 Zürich (Switzerland)
E-mail: erickm.carreira@org.chem.ethz.ch
Homepage: http://www.carreira.ethz.ch

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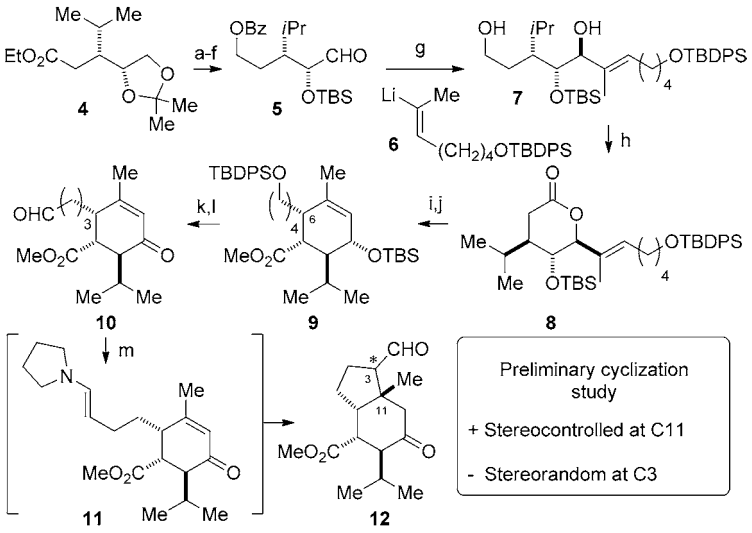
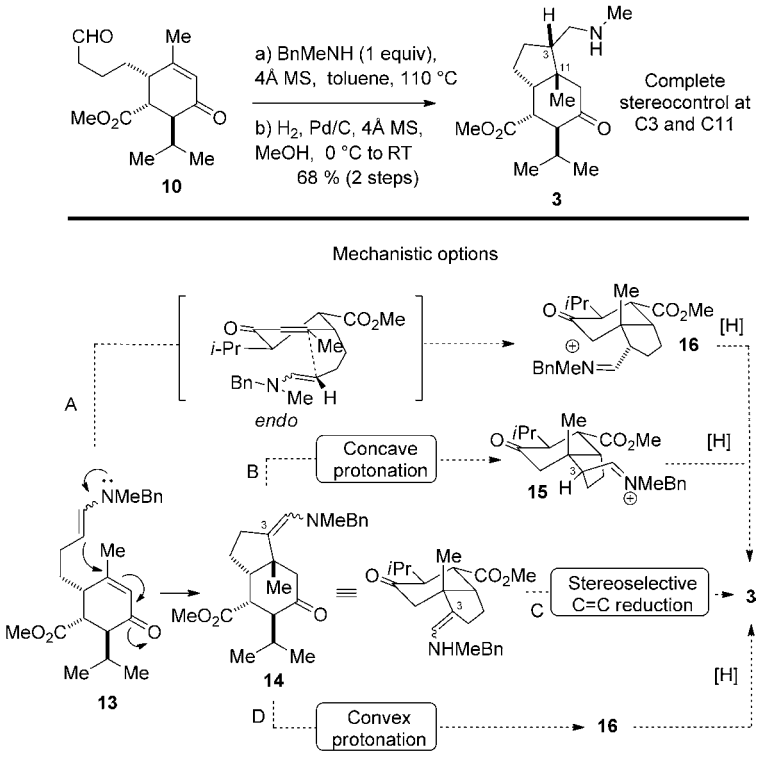


Scheme 2. Reagents and conditions: a) $LiAlH_4$, THF, 0 °C, 95 %; b) PhCOCl, DMAP, NEt_3, CH_2Cl_2, 0 °C to RT; c) AcOH, H_2O, 50 °C; d) *t*$BuMe_2SiCl$, DMAP, imidazole, CH_2Cl_2, 0 °C to RT, 77 % over three steps; e) HF·pyridine, THF, 0 °C to RT, 84 %; f) $(COCl)_2$, Me_2SO, NEt_3, −78 °C to RT, 98 %; g) **9**, 0 °C; EtMgBr, 81 %, d.r. (*anti*/*syn*) = 2.2:1; h) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, 0 °C to RT, 88 %; i) *i*Pr_2NLi, Me_3SiCl, THF, −78 °C to RT; toluene, 110 °C; j) Me_3SiCHN_2, C_6H_6, MeOH, 6 °C to RT, 95 % over two steps; k) HF·pyridine, THF, 0 °C to RT, 88 %; l) PCC, celite, CH_2Cl_2, RT, 76 %; m) C_5H_9N, C_6H_6, 4 Å molecular sieves, 80 °C, 65 %, d.r. = 2:1. TBS = *tert*-butyldimethylsilyl; TBDPS = *tert*-butyldiphenylsilyl; TEMPO = 2,2,6,6-tetramethylpiperidine-1-oxyl; PCC = pyridinium chlorochromate; DMAP = 4-dimethylaminopyridine.

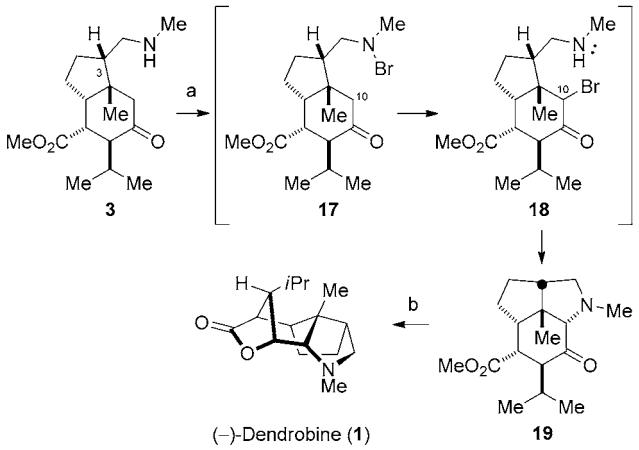
Thus, treatment of **10** with *N*-methylbenzylamine followed by exposure to H_2/Pd led to the selective formation of **3** in high diastereoselectivity (Scheme 3).[23] Overall, this sequence not only allowed the diastereoselective formation of the crucial C3–C11 bond, but also for the elegant introduction of the desired pendant amine in 68 % yield.[24]

The mechanistic possibilities for the sequence that may lead to the selective formation of **3** are shown in Scheme 3. In the first possibility (pathway A), the direct formation of **3** with complete control at the C3 and C11 positions, in principle, could occur during the cyclization. However, this would require that the enamine side chain be oriented *endo* during the course of the cyclization. As an alternative, following cyclization of **13**, the first-formed iminium cation undergoes proton loss to give enamine **14**. Nonselective protonation furnishes diastereomeric intermediates **15** and **16** (pathways B or D: concave versus convex protonation) followed by preferential and rapid reduction of **16**. In effect, the sequence affording **3** would correspond to a dynamic kinetic resolution process. As a third mechanistic option (pathway C), reduction of C=C in **14** from the convex face would directly and stereoselectively produce **3**. We favor the fourth option (pathway D) in which stereoselective protonation of **14** gives **16**, which then undergoes reduction to amine **3**. This is consistent with an observation that we have made involving aldehyde **12** (Scheme 2). In one experiment, we noted that **12** could be isolated with great care as a mixture of diastereomers (5:1), before it rapidly undergoes epimerization. If the formation of **16** occurs with high facial selectivity in the protonation step, subsequent reduction of the iminium group would produce an amine that is no longer susceptible to epimerization at the C3 position. Consequently, the coupling of the two reactions in a cascading sequence provides a shunt mechanism that precludes the loss of stereochemical information.

Having constructed the carbocyclic core, completion of the synthesis required the installation of the pyrrolidine. We reasoned that this oxidation sequence could be best accomplished by bromination at the Cα position of the ketone, followed by nucleophilic displacement by the pendant amine (Scheme 4). PHT proved to be a highly regioselective bromination agent at C10.[25] We speculate that the selectivity arises by the kinetic generation of *N*-bromoamine **17**, which leads to directed, regioselective ketone bromination to give **18**. This was followed by ring closure in the same pot, albeit to a maximum of 50 % conversion. We then observed that addition of DMAP after bromination led to complete conversion into **19** in 63 % yield. We hypothesize that DMAP might not merely act as a base, but that it could also induce epimerization at the C10 position, such that the C–Br bond is correctly aligned for S_N2 displacement. Furthermore, DMAP may also



Scheme 3. Cascade sequence to construct the core structure of (−)-dendrobine (**1**).



Scheme 4. a) PHT (1.1 equiv), THF, RT; DMAP (1 equiv), 63%; b) $NaBH_4$, *i*PrOH, RT to 50°C, 65%. PHT = Pyrrolidone hydrotribromide.

serve as a nucleophilic catalyst over the course of the substitution reaction. The conversion of amino ketone **19** into (−)-dendrobine (**1**) was accomplished by reduction with $NaBH_4$ followed by lactonization at elevated temperature.[26]

In summary, we have reported an asymmetric total synthesis of (−)-dendrobine (**1**) in 18 linear steps and 4.0% overall yield. As such, the route delivers the targeted natural product in a yield that is considerably improved over any previous syntheses. The salient features of synthesis include (1) the efficient construction of the central cyclohexane core by a Ireland-Claisen rearrangement, (2) a cascading series of reactions proceeding through a conjugate enamine addition/hydrogenation sequence to install the quaternary center as well as the pendant methyl amino group, and (3) regioselective ketone bromination followed by pyrrolidine formation. To our knowledge, the enamine conjugate addition to a β-disubstituted enone is the first example of its kind to install a quaternary stereocenter. The observations with the cascading sequence of reactions involving in situ reduction of the final intermediate underscores the advantages that may be accrued when executing multiple reactions in sequence when the individual steps may be otherwise problematic. Further studies to extend the reported strategy to the total synthesis of structurally related alkaloids are underway.

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[15] Vinyl lithium **10** was obtained in four steps from 5-hexynol (see the Supporting Information for details).
[16] The configuration of the allylic alcohols were assigned based on NMR studies (NOESY), following conversion to **8** (see Supporting Information for details).
[17] Interestingly, the ratio of diastereomers obtained from addition at −78 °C was 1.2:1 (*anti*/*syn*) in a comparable combined yield.
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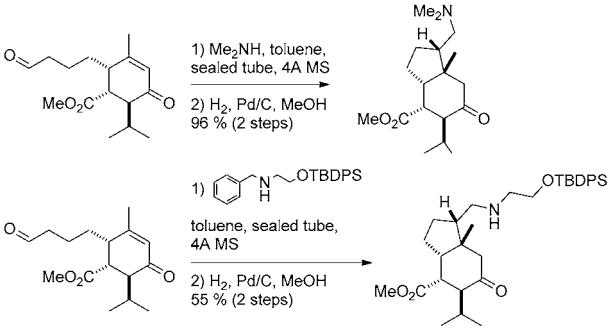
[21] PCC proved to be very effective for this transformation, as, for example, the Dess–Martin periodinane led to considerable amounts of elimination of the allylic alcohol resulting in isomeric diene products.
[22] Equilibration to the desired isomer was not successful under either basic or acidic conditions.
[23] According to ^{1}H NMR analysis, the diastereomeric ratio is greater than 10:1.
[24] The cyclization cascade can be made to work with other amines as shown below:
[25] Bromine in acetic acid led to a regioisomeric mixture of brominated compounds. For a previously reported regioselective



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[26] This is a slightly modified procedure adapted from Refs. [8c] and [8e].

