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TOTAL SYNTHESIS OF THE POLLEN-GROWTH INHIBITOR (-)-EMENIVEOL. ASSIGNMENT OF ABSOLUTE STEREOCHEMISTRY

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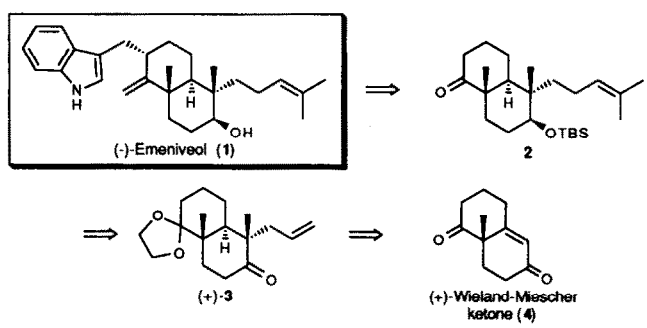
Abstract: The total synthesis of emeniveol, a pollen growth inhibitor, is described and its absolute stereochemistry was determined using (+)-Wieland-Miescher ketone as the starting material.

In 1992, Kimura and co-workers[1] reported the isolation of the pollen-growth inhibitor (-)-emeniveol (**1**) from the fungus *Emericella nivea*. The structure and relative stereochemistry of **1** were unambiguously determined by single-crystal X-ray analysis. Herein we disclose a short, *effective* synthesis of scalemic (-)-emeniveol which has permitted assignment of the absolute configuration.

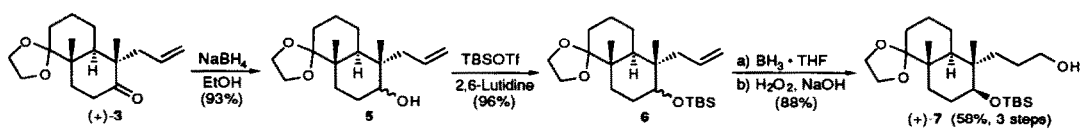
Our retrosynthetic analysis is outlined in Figure 1. We envisioned that emeniveol (**1**) could be generated via the coupling of ketone **2** with a suitably protected 3-methylindole derivative. Ketone **2** in turn would derive from ketal (+)-**3**, an intermediate exploited to great advantage in our total synthesis of (-)-paspaline;[2] ketal (+)-**3** is available in three steps from (+)-Wieland-Miescher ketone (**4**).

Figure 1



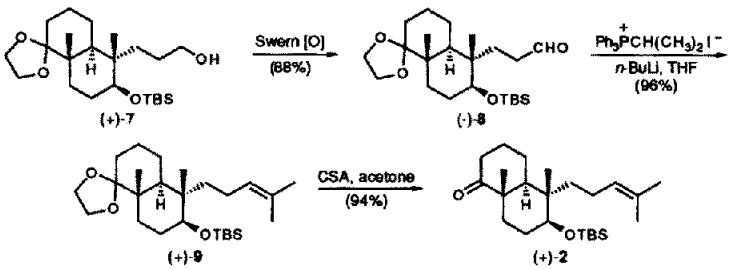
Reduction of (+)-**3** with $NaBH_4$ afforded an inseparable 4:1 mixture of β and α alcohols **5** (Scheme I) which upon treatment with TBS triflate provided the corresponding silyl ethers **6**. Following hydroboration-oxidation, the desired epimer (+)-**7** was easily isolated via flash chromatography (silica gel; 1:9 ethyl acetate/hexane) in 58% yield overall from **3**.

Scheme I



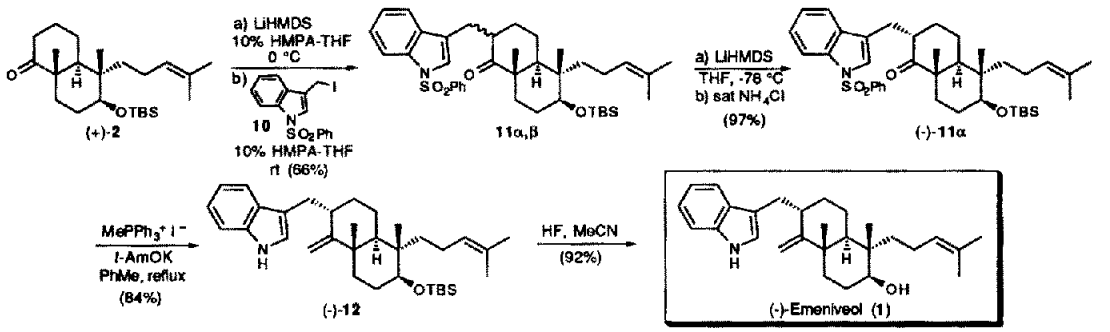
Swern oxidation of (+)-**7** then furnished aldehyde (-)-**8** in 88% yield (Scheme II), which in turn was subjected to Wittig reaction with the ylide generated from isopropyltriphenylphosphonium iodide and *n*-butyllithium (-78 → 0 °C) to furnish (+)-**9** in 96% yield. Deketalization afforded ketone (+)-**2** (92% yield).

Scheme II



Alkylation of ketone **2** was achieved by reverse addition of the lithium enolate of **2** (1.2 equiv LiHMDS, 10% HMPA, THF, 0 °C) to *N*-phenylsulfonyl-3-(iodomethyl)indole[3] (**10**) in 10% HMPA-THF at room temperature. The reaction was very sensitive to both the order and rate (2 drops/sec) of addition, furnishing the desired material (**11**α,β) in 66% yield as a 1:1 mixture of diastereomers. The mixture could be completely converted to the desired α isomer by deprotonation with LiHMDS in THF (-78 °C) and subsequent quenching with a saturated solution of aqueous ammonium chloride (97% yield). High-temperature Wittig methylenation also unmasked the indole moiety, generating (-)-**12** in 84% yield.[4] Finally, removal of the TBS group entailed exposure to HF in MeCN for 30 min at ambient temperature (92%).

Scheme III



Synthetic (-)-emeniveol (**1**) was identical [TLC, mp 177.5-178.5 °C (lit.[1] 179 °C), mmp 176.5-178.5 °C, ^{1}H and ^{13}C NMR analysis, and optical rotation ($[\alpha]_D^{20}$ -87.5° (*c* 0.53, MeOH); lit.[1] $[\alpha]_D^{20}$ -91° (*c* 1.0, MeOH))] with an authentic sample generously provided by Professor Clardy.[1]

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References

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