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A NOVEL APPROACH TO (+)-YOHIMBINE

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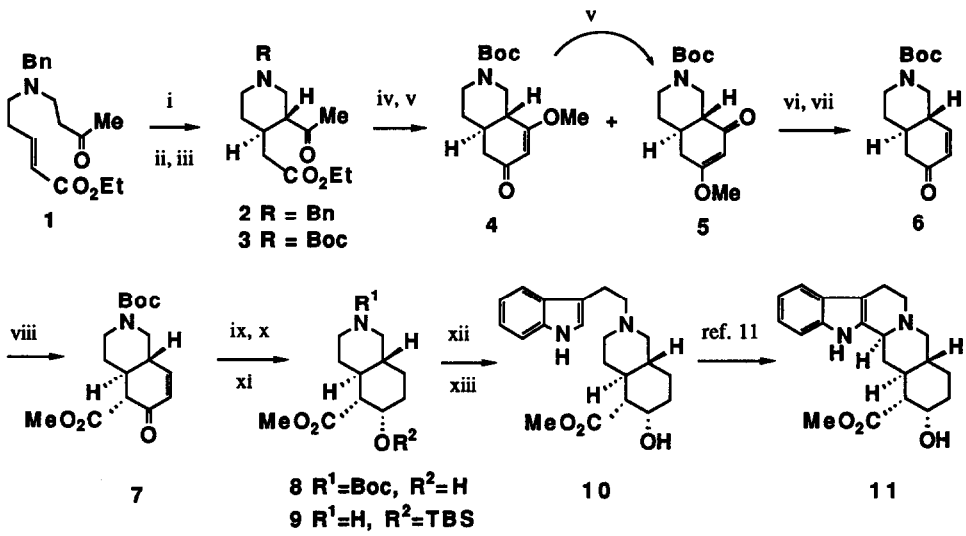
Summary: *The synthesis of (+)-yohimbine was achieved by the reaction sequence involving the asymmetric intramolecular Michael reaction to form the D-ring piperidine system and subsequent formation of the E ring skeleton followed by regio- and stereo-selective introduction of the methoxycarbonyl and hydroxyl on the ring E.*

Previous studies in our laboratory have established the design of the substrate for an asymmetric intramolecular Michael reaction and accomplished the preparation with high enantioselectivity of the functionalized piperidine system as chiral building blocks for several alkaloids.[1] In continuing studies on application of this method to the synthesis of biologically active natural products, we tried to synthesize *Rauwolfia* alkaloids which have received considerable attention because of their varied range of pharmacological activities.[2] We present here the first report of an asymmetric synthesis of (+)-yohimbine (**11**),[3,4] the most important member of the yohimboid class of alkaloids.

Our initial effort was focussed on increasing the enantiomeric excess (ee) of the piperidine derivative **2** (*ca.* 90% ee) derived from the acyclic compound **1** by the asymmetric intramolecular Michael reaction,[1] and recrystallization of its hydrobromide from dry ethanol increased the ee up to 98%.[5] Debenzylation of **2** over $Pd(OH)_2$ under a hydrogen atmosphere followed by treatment with di-*t*-butyl dicarbonate [$(Boc)_2O$] gave the urethane **3**[6] in 92% yield. Cyclization of **3** by treatment with lithium diisopropylamide (LDA) smoothly proceeded *via* kinetic deprotonation to give a bicyclic compound in 99% yield, which on *p*-toluenesulfonic acid (*p*-TsOH) catalysis in dry methanol afforded a 1:3.7 mixture of the vinylogous ethers **4** and **5** in 85% combined yield. Since the minor ether **4** was equilibrated into the parent mixture under the same conditions as mentioned above, only the desired isomer **5** was eventually obtained by repetition of this procedure. Reduction of **5** with diisobutylaluminum hydride (DIBAL) and subsequent treatment of the resulting alcohol with a catalytic amount of *p*-TsOH gave the α,β-unsaturated ketone **6**, $[\alpha]^{26}_D$ -55.6° (*c* 1.16, $CHCl_3$), in 72% yield. The treatment of the lithium enolate of **6** with methyl cyanoformate [7,8] afforded the β–keto ester **7** in 84% yield, which on catalytic hydrogenation over 5% Pd-C under a hydrogen atmosphere followed by reduction with L-Selectride® gave the desired alcohol **8** as a sole product in 79% yield. The treatment of **8** with *t*–butyldimethylsilyl trifluoromethanesulfonate (TBSOTf)[9] caused selective cleavage of the *t*-butoxycarbonyl (Boc) group and spontaneous protection of the hydroxyl to give the secondary amine **9** in 91% yield. Alkylation of **9** with tryptophyl bromide followed by desilylation (HF-MeCN) afforded 2,3-seco-yohimbine (**10**), m.p. 116-118°C, $[\alpha]^{26}_D$ +43.8°(*c* 1.07, MeOH), in 88% yield. The structure of **10** was confirmed by direct comparison with an authentic sample which was derived from natural yohimbine.[10,11] Total synthesis of (±)-yohimbine *via* the racemate of **10** has already been accomplished by G. Stork and coworkers.[12] S. Sakai and coworkers[11] have also reported the conversion of **10** to (+)-yohimbine (**11**) by a similar method. Then, to our knowledge, this

is the first formal asymmetric synthesis of (+)-yohimbine (**11**) to be reported. Furthermore, since the enantiomer of **2** has been obtained with high enantioselectivity,[1] this method also constitutes an enantioselective synthesis of (-)-yohimbine.



(i) (+)-α-phenylethylamine, THF, molecular sieves 5A, 5° C; (ii) H_2, $Pd(OH)_2$; (iii) $(Boc)_2O$, pyridine, Et_2O; (iv) LDA, THF, -78°C; (v) *p*-TsOH, MeOH, rt; (vi) DIBAL, toluene, -78°C; (vii) *p*-TsOH, Et_2O; (viii) LDA, THF, -78° C and then methyl cyanoformate; (ix) H_2, 5% Pd-C, MeOH; (x) L-Selectride®, THF, -78°C; (xi) TBSOTf, CH_2Cl_2, rt; (xii) tryptophyl bromide, K_2CO_3, MeCN, reflux; (xiii) HF, MeCN, rt.

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5. The optical purity of the recrystallized piperidine derivative **2** was determined by examining the ^1H nmr of the corresponding (+)-MTPA ester of the alcohol which was selectively obtained by debenzylation-methoxycarbonylation of **2** and subsequent reduction with $NaBH_4$.
6. All new compounds gave satisfactory 270 Mz ^1H nmr, ir, and high resolution mass spectra and/orelemental analyses.
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