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TOTAL SYNTHESIS OF α-YOHIMBINE

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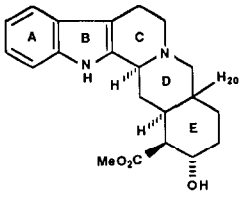
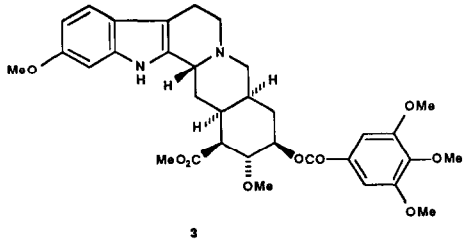
Abstract. A facile total synthesis of the indole alkaloid α-yohimbine (**1**) from the hydroisoquinoline derivative **5** has been completed.

The yohimbine family of indole alkaloids constitutes a medicinally and structurally important class of naturally occurring bases,[2] of which α-yohimbine (**1**), yohimbine (**2**), and reserpine (**3**) are representative members. Although yohimbine (**2**)[3] and reserpine (**3**)[4] have been the objects of extensive synthetic investigations, surprisingly α-yohimbine (**1**)[5] has received only limited attention. Recently novel derivatives of several yohimbine alkaloids bearing unsaturation at C(19) such as 19,20-dehydroyohimbine (**4**)[6] have become the focus of attention. During the course of the past several years, a principal objective in our laboratories has been the development of a general entry to the pentacyclic indole alkaloids,[7] and it occurred to us that the hydroisoquinoline derivative **5**, which was an intermediate in our recent total synthesis of reserpine (**3**),[4] might also serve as a viable precursor of the fully intact D/E ring subunit required for the total syntheses of α-yohimbine (**1**) and 19,20-dehydroyohimbine (**4**). A summary of investigations directed to reduce this strategy to practice forms the basis of the present account.



1: α-H_{20}
2: β-H_{20}



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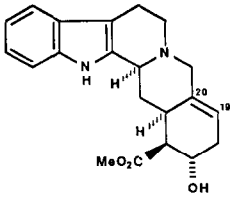

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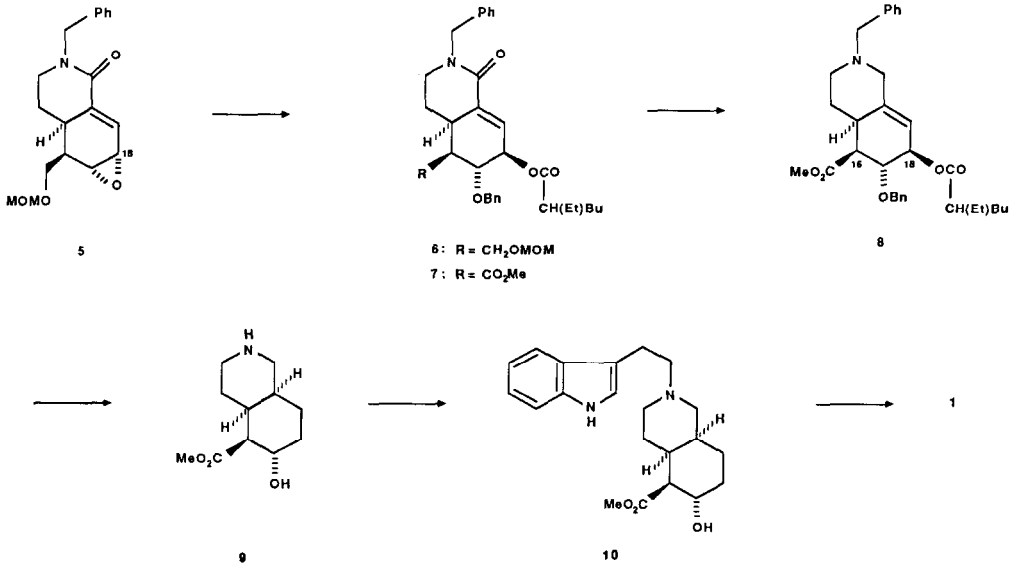
Initial attempts to elaborate the E ring by reductive opening of the epoxide moiety at C(18) of **5**, which is readily available from propargyl alcohol in 41% overall yield (8 steps),[4,7c] using various hydride reagents or by catalytic hydrogenation led only to the production of complex mixtures. On the other hand, acid-catalyzed opening of the epoxide [BuCH(Et)COOH/BuCH(Et)COOLi, DME, reflux, 12 h; 90%] followed by benzylation [BnBr, Ag_2O, $CaCO_3$, 50 °C, 3.5 d; 76%) of the intermediate alcohol proceeded smoothly to afford **6** (Scheme 1).[8] Selective removal of the protecting group from the hydroxyl function at C(16) (p-TsOH, MeOH, 40 °C, 30 h; 86%) and conversion of the resulting primary alcohol into the corresponding methyl ester [(a) PDC, DMF, RT, 20 h; 84%. (b) CH_2N_2, Et_2O/MeOH (2:1), 0 °C; 96%] gave **7**. Chemoselective reduction of the lactam moiety (AlH_3, THF, -70→-25 °C, 2 h; 89%) afforded the intermediate tertiary amine **8**. Subjection of **8** to the conditions of catalytic hydrogenation [H_2/1 atm, 20% $Pd(OH)_2$/C, HOAc/cat. H_2SO_4, 60 h] resulted in the simultaneous hydrogenolysis of the benzyl protecting groups on nitrogen and on the hydroxyl group at C(17), hydrogenolysis of the allylic acyloxy group at C(18) and stereoselective reduction of the carbon-carbon double bond at C(19) to deliver the secondary amine **9**, which underwent facile N-alkylation with tryptophyl bromide (K_2CO_3, DMF, 55 °C, 5 h) to provide 2,3-seco-2,3-dihydro-α-yohimbine (**10**) in 55% overall yield. Subsequent oxidative cyclization[9] [$Hg(OAc)_2$/EDTA-2Na (1:1), EtOH/H_2O (1:2), reflux, 3 h]

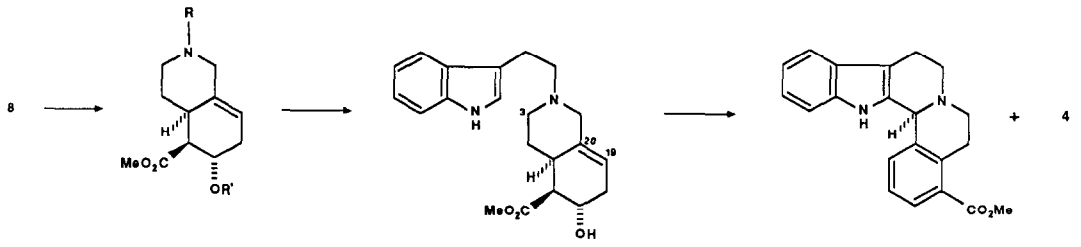
Scheme 1



of **10** followed by stereoselective hydride reduction of the intermediate iminium salts [$NaBH_4$, MeOH/H_2O (9:1), pH 6-7, 1 h] then provided α-yohimbine (**1**)[10] in 31% overall yield together with an equal amount of the inside isomer.

Since the hydroisoquinoline **8** bears the unsaturation at C(19) present in the dehydroyohimbine alkaloids, it seemed a reasonable intermediate for the total synthesis of 19,20-dehydroyohimbine. In the event, hydrogenation/hydrogenolysis of **8** under conditions slightly different from those employed previously [H_2/1 atm, 20% $Pd(OH)_2$/C, HOAc/5% H_2SO_4, 4 h] afforded the unsaturated tertiary amino acetate **11**, which was readily converted to the secondary amino alcohol **12** [(a) $MeCHClOCOCl$,[11] $ClCH_2CH_2Cl$, reflux, 1 h. (b) 1N HCl/MeOH, reflux, 1 h] in 62% overall yield from **8** (Scheme 2). Although N-alkylation of **12** with tryptophyl bromide as before proceeded smoothly to give **13** in 75% yield, the oxidative cyclization of **13** according to established procedures produced the aromatic inside derivative **14**[12] as the major product (57%) together with only small quantitites (<5%) of a compound which has been tentatively identified as the desired 19,20-dehydroyohimbine (**4**). Thus, although it has proven feasible to elaborate the dehydro D/E ring subunit **12** from **5** as planned, attempts thus far to parlay this success into the total synthesis of the dehydroyohimbine alkaloid **4** have been sabotaged by the inability to functionalize the seco-derivative **13** selectively at C(3) by oxidative methods. Alternate approaches to **4** via other derivatives of **12** are under current investigation.

Scheme 2



11: R = Bn, R' = Ac
12: R = R' = H

13

14

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1. Recipient of a National Institutes of Health (National Cancer Institute) Research Career Development Award (1980-1985).

2. For leading references and reviews of the monoterpenoid alkaloids of the indole family, see: Saxton, J. E. in "Specialist Periodical Reports, The Alkaloids", The Royal Society of Chemistry, Burlington House: London, 1983; Vol. 13, pp. 221-237. See also in Vol. 1-12.

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8. The structure assigned to each compound was fully in accord with its spectral (^{1}H and ^{13}C NMR, IR, MS) characteristics. Analytical samples of all new compounds were obtained by distillation, recrystallization or preparative HPLC and gave satisfactory combustion analysis (C, H, N) and/or identification by high resolution mass spectrometry. All yields are based upon isolated, purified materials that were homogeneous as determined by capillary GLC or HPLC.

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10. The α-yohimbine (1) thus obtained was identical (360-MHz ^{1}H, ^{13}C NMR, IR, MS, TLC) with an authentic sample purchased from Accurate Chemicals and Scientific, Westbury, NY.

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12. The formation of **14** was previously observed in an oxidative cyclization of 2,3-seco-2,3-dihydroyohimbine. See Aimi, N.; Yamanoka, E.; Endo, J.; Sakai, S.; Haginiwa, J. Tetrahedron **1973**, 29, 2015.

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