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AN ENANTIOSELECTIVE SYNTHESIS OF (-)-ALLOYOHIMBANE

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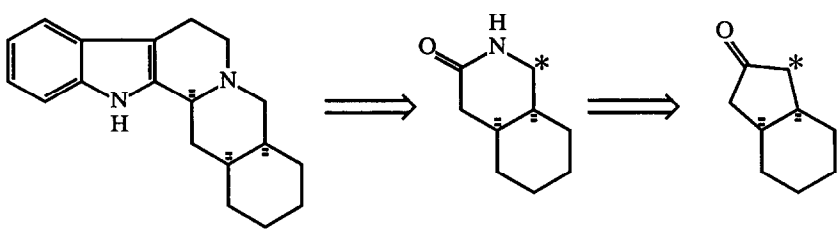
Summary: A conceptually novel total synthesis of (-)-alloyohimbane is reported. The key step utilizes a group-selective nitrogen insertion process on a meso bicyclic ketone.

The alkaloids of the yohimbine and reserpine families have inspired a number of imaginative synthetic efforts.[1] This is both due to their challenging and intricate structures and their prominence as medicinal agents and pharmacological tools.[2] However, despite this activity spanning many years, the asymmetric synthesis of this class of natural products has received only recent attention.[3] I wish to introduce a conceptually novel approach to this important ring system in optically active form by way of an enantiospecific total synthesis of the prototype alkaloid, (-)-alloyohimbane.

An obvious precursor to the pentacyclic ring skeleton of (-)-alloyohimbane **1** is the lactam **2**, which contains the crucial CD cis ring fusion and an amide functionality suitably disposed for the regiospecific annulation of the indole moiety. An additional advantage inherent in the use of lactam **2** is the ready adaptability of the sequence to analogs containing bioisosteric replacements of the aromatic portion.[4] This cis-fused, bicyclic lactam can be seen to arise from the known 2-indanone **3** via a Beckmann-type ring expansion reaction.

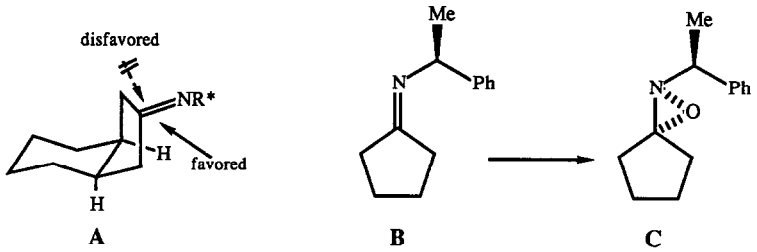


1 **2** **3**

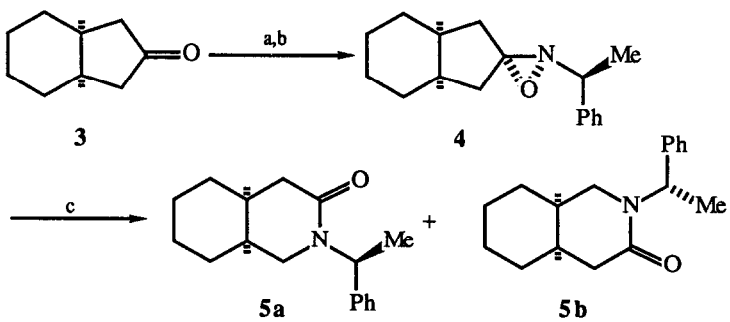
The key feature of the present strategy is the recognition that lactam **2** can be obtained in optically active form if a single enantiotopic methylene group in **3** (starred) preferentially migrates to nitrogen in such a rearrangement reaction. A protocol to accomplish this transformation is under current investigation in these laboratories,[5] wherein a symmetrical ketone is converted to an axially dissymmetric spirooxaziridine, which subsequently undergoes photochemical rearrangement to afford a chiral lactam. The successful realization of the sequence of **3**→**2** represents the first asymmetric extension of the method to a meso cyclopentanone substrate.[6]

In order to successfully realize this plan, it was necessary to consider two stereochemical variables in the application of the asymmetric nitrogen insertion process. Thus, it was hoped to take advantage of the well-known proclivity of a reagent to approach from the exo (convex) face of bicyclic structures (cf. **A**). In addition, it has

been established that imines containing an asymmetric nitrogen substituent undergo oxidation to afford oxaziridines with high diastereoselectivity to afford the major isomer shown (**B** to **C** + isomer, ratio 87 : 13).[7] Taken together, these considerations implied that one stereoisomeric, configurationally stable oxaziridine[8] would predominate out of the four possible isomers. Finally, and most critically, it was expected that the known tendency for the carbon anti to the lone pair in cyclic oxaziridines to preferentially migrate to nitrogen under photolytic conditions would prevail in an oxaziridine derived from a substituted cyclopentanone.[5]



In the event, ketone **3**[9] was converted to a mixture of imines by treatment with (S)-(–)-α-methylbenzylamine under reflux (toluene, 16 h, Dean-Stark trap). The imines thus formed were not isolated, but rather treated in situ with m-chloroperoxybenzoic acid (mCPBA)(toluene, -78°C, 0.5 h) to provide an inseparable mixture of oxaziridines **4** in 86% overall yield. Four isomers could be detected by ^{13}C NMR spectroscopy in an approximately 66 : 17 : 10 : 7 ratio The major component of the mixture is presumed to be the isomer depicted due to the aforementioned considerations.



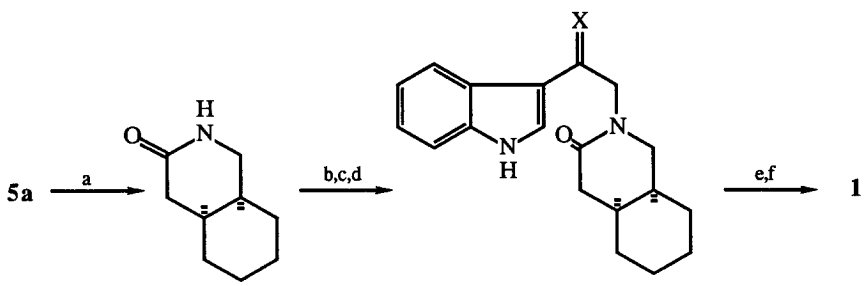
Scheme 1

Reagents: (a) (S)-(-)-α-methylbenzylamine, toluene, reflux, 16 h. (b) mCPBA, toluene, -78°C (86-91%, two steps). (c) hv, cyclohexane, 2537 Å (52%, **5a**:**5b** = 2.1 : 1).

Photolysis (Rayonet reaction chamber, 2537 Å, cyclohexane, 6 h) gave rise to a 2.1 : 1 mixture of lactams **5a,b** which could be readily separated by silica gel chromatography (47-53%). The complete stereostructure of the major isomer was ultimately secured by its conversion to (–)-alloyohimbane (vide infra). These results show that the overall conversion of **3** to **5** occurs with stereoselectivity that is consistent with with the initial hypotheses. These points are currently under closer scrutiny, as are a number of schemes designed to improve the overall efficiency of the sequence.

The conversion of the key chiral lactam **5a** to alloyohimbane was carried out in a straightforward manner. Compound **5a** was converted to the N-unsubstituted lactam **2** ($[a]_D$ = –30.9° (c = 1.02, MeOH)) by brief exposure to sodium in liquid ammonia in 77-86% yield based on recovered starting material. Alkylation was achieved by the generation of the sodium salt of **2** by the action of sodium hydride in dimethylformamide followed

by the rapid addition of 3–chloroacetylindole[10] (53%). Deoxygenation was carried out using the protocol of Fujii:[11] treatment with sodium borohydride in ethanol (24 h, RT) followed by hydrogenolysis (Pd/C, EtOH, 0.01 molar equivalents $HClO_4$, 1 h, 42% overall yield). The final Bischler-Napieralski cyclization was performed in the standard manner ($POCl_3$, benzene, reflux; $NaBH_4$, methanol, 59 % for two steps). In this way was obtained (–)–alloyohimbane, mp 155-156°C , $[a]_D$ = -164° (c = 0.5, pyridine) (lit.[3d,12] 156°C, $[\alpha]_D$ = -166° (c = 0.5, pyridine)). Spectral data (IR, ^{13}C NMR) were in complete agreement with literature[12] values.



Scheme 2

Reagents: (a) Na, NH_3, (77-86% based on recovered starting material). (b) NaH in DMSO, then 3-(chloroacetyl)indole (52%). (c) $NaBH_4$, ethanol, 24 h. (d) 1 atm. H_2, Pd/C, ethanol, $HClO_4$ (0.01 molar equivalent) (42%, two steps). (e) 1 equivalent $POCl_3$, benzene, reflux. (f) $NaBH_4$, methanol (59%, two steps).

The utility of a group-selective asymmetric nitrogen insertion reaction as a tool for alkaloid synthesis has been demonstrated in the context of a total asymmetric synthesis of (-)-alloyohimbane. Work to extend this methodology to the synthesis of more complex members of the yohimbine and reserpine families, and to improve the selectivity of the asymmetric nitrogen insertion reaction is in progress.

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