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STUDIES ON THE SYNTHESIS OF *STEMONA* ALKALOIDS; STEREOSELECTIVE PREPARATION OF THE HYDROINDOLE RING SYSTEM BY OXIDATIVE CYCLIZATION OF TYROSINE

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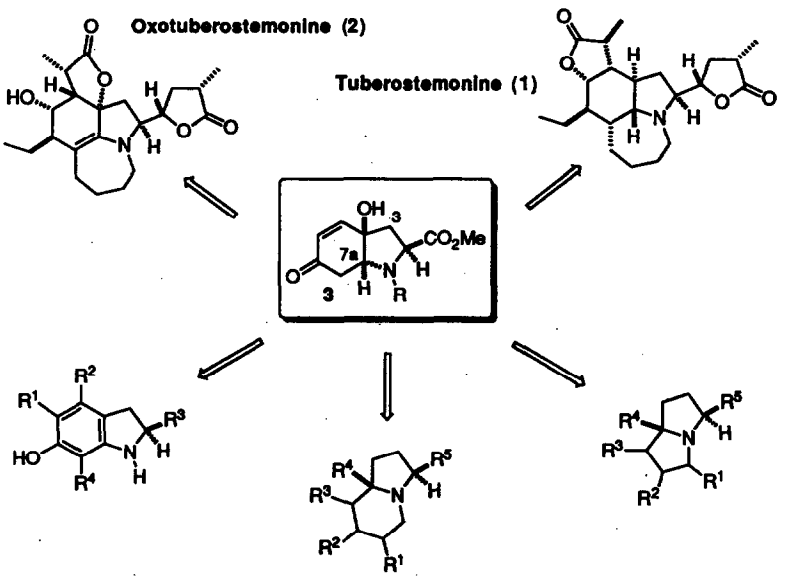
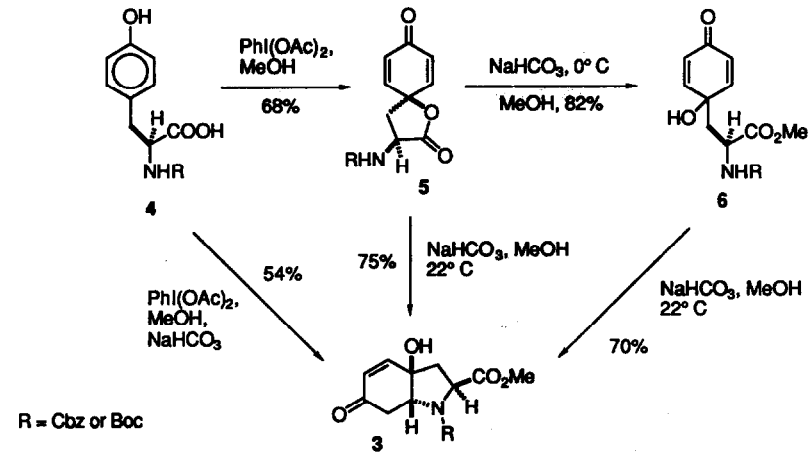
Abstract: The core hydroindole ring system of the *Stemona* alkaloids was prepared by oxidation of tyrosine with a hypervalent iodine reagent followed by a diastereotopic group-selective intramolecular conjugate addition. Further transformations illustrate the versatility of the highly functionalized hydroindolenone **3** for alkaloid synthesis.

As part of our studies directed toward the total synthesis of *Stemona* alkaloids tuberostemonine (**1**) and oxotuberostemonine (**2**),[1] we required an efficient approach for the preparation of key intermediate **3**. Azabicycle **3** was envisioned to be an ideal building block for the preparation of highly substituted indole, indolizidines and pyrrolizidine ring systems. Especially for the preparation of a variety of *Stemona* alkaloids, the dense functionalization at C(2) through C(7a) of hydroindole **3** would enable a straightforward stereoselective assembly of the multiple stereocenters and attached ring systems present in these natural products.[2]

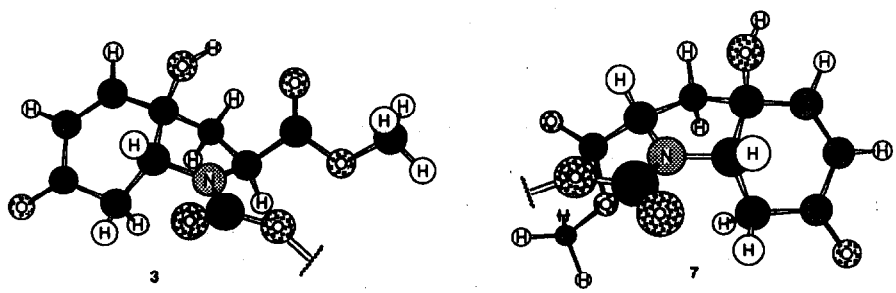


In this letter we report a highly stereoselective preparation of hydroindolenone **3** and related derivatives from very readily available tyrosine. After some optimization of the oxidizing reagent, we found that N-protected tyrosine derivatives **4** were efficiently cyclized to the corresponding

spirolactones **5** by treatment with a slight excess of iodobenzene diacetate.[3,4] The spiro carbon in **5** represents an example of a chirotopic, nonstereogenic center.[5] However, methanolysis of lactone **5** at 22° C in the presence of $NaHCO_3$ cleanly led to the desired bicycle **3** as the only detectable diastereomer by ^1H and ^{13}C NMR and GC analysis! In contrast, methanolysis at 0° C provided exclusively dienone **6**, which was indefinitely stable at room temperature in neat form and slowly converted back to the spirolactone **5** in solution. Formation of the desired bicycle **3** was also effected directly by tyrosine oxidation in the presence of bicarbonate.



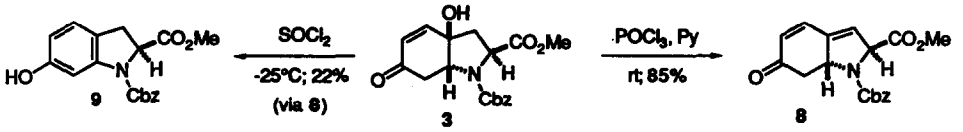
At present, the reasons for the exceptional selectivity in the novel diastereotopic end group differentiation in the conversion of **5** and **6** to **3** are not completely understood. Molecular Mechanics calculations[6] indicate only an approx. 1 kcal/mol stabilization of exo isomer **3** vs. the (experimentally not observed) endo isomer **7**. Possibly, the presence of an intramolecular H-bond between the tert. alcohol and the ester functionality in **3** is responsible for the observed high preference for formation of the exo isomer (in the absence of H-bonding interactions, isomer **7** is of 1.1 kcal/mol lower steric energy than isomer **3** according to MM2 calculations). Whereas intramolecular Michael additions have previously been applied for alkaloid synthesis,[7] the conversion of **5** and **6** into **3** represents the first example of a highly diastereotopic group-selective version of this process.[8,9]



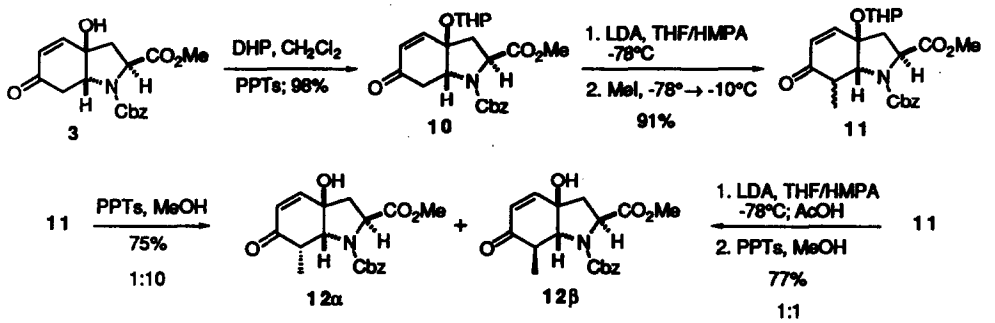
The relative stereochemistry of hydroindolenone **3** was assigned by a series of ^1H NMR double-resonance experiments. As the determination of coupling constants at room temperature was complicated by the presence of two carbamate bond rotamers of **3** in approx. 2:3 ratio, all NMR experiments were performed at 100 °C in DMSO-d_6 solution. Complete coalescence with **3** (R=Cbz)

was observed at 70 °C. The correlation between the experimentally determined coupling constants and the expected values for the calculated geometry of **3** is satisfactory.[10,11] Moreover, the presence of a long-range *W*-coupling between H-C(7a) and Hβ-C(3) (^4J = 0.8 Hz) confirms the proposed stereochemistry for **3**.

The possibility for functionalization at C(3) and C(7a) of bicycle **3** and the ease and direction of elimination of the tertiary alcohol group was explored by treatment with $POCl_3$ and $SOCl_2$. In both instances, an initial kinetically controlled elimination to give dienone **8** was observed. With $SOCl_2$, **8** was subsequently slowly converted into dihydroindole **9**, whereas no further reaction was observed under $POCl_3$ conditions.



In order to determine the critical reactivity of the lithium enolate of **3** toward functionalization at C(7), the tertiary alcohol was protected with dihydropyran. Deprotonation of enone **10** with LDA in a mixture of THF and HMPA (10%) and addition of methyl iodide led indeed to the α-methylated ketone **11** in excellent yield. In the absence of electrophiles, the lithium dienolate underwent β-elimination only at temperatures > 0 °C.[12] The presence of a dipolar solvent, however, was crucial for the success of this alkylation. Cleavage of the THP ether in **11** provided ketones **12α** and **12β**, easily separable by silica gel chromatography, in a ratio of approx. 1:10. The configuration at C(7) of these epimers was unambiguously assigned by chemical shift analysis, $^3J_{HH}$ analysis,[10] and 1D NOE studies.[13] Reenolization of **11**, followed by kinetic protonation with acetic acid at -78 °C, provided a 1:1 ratio of C(7) isomeric ketones in 77% yield after hydrolysis.



The ease of preparation of hydroindolenone **3** directly from N-protected tyrosine and the straightforward further modification provide a versatile strategy for the use this bicycle as a highly functionalized building block for alkaloid synthesis. Further progress toward the total synthesis of *Stemona* alkaloids will be reported in due course.

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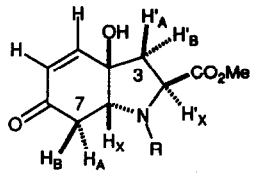
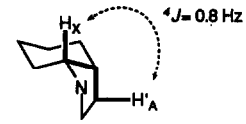
11. 

	J_{HH} (obs)	$^3J_{HH}$ (calc)
J_{AB}	= 16.0 Hz	
J_{AX}	= 9.5 Hz	= 11.1 Hz
J_{BX}	= 5.9 Hz	= 5.3 Hz
J'_{AB}	= 12.5 Hz	
J'_{AX}	= 2.4 Hz	= 1.6 Hz
J'_{BX}	= 9.0 Hz	= 8.8 Hz



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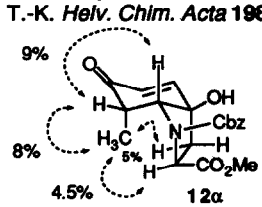
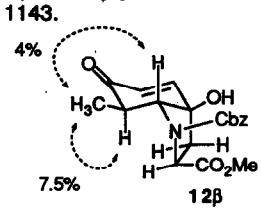


12α



12β

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