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THE SYNTHESIS OF (+)- AND (-)-1-BENZOYL-1,2,2a,3,4,5-HEXAHYDRO-BENZ[*cd*]INDOL-4-AMINE, and PREPARATION OF LY228729.

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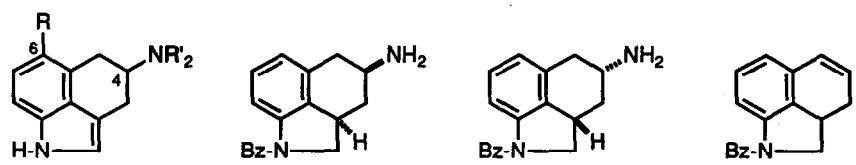
Summary: Racemic epoxide 5 was reacted with S-Phenylethylamine to afford diastereomers 6 and 7, from which amino alcohol 6 could be isolated directly. Aziridine formation and tandem-hydrogenolysis provided optically pure primary amine 2 (31% from racemic 4), which was further elaborated to LY228729 (15), an interesting $5HT_{1a}$ receptor agonist.

6-Substituted 1,3,4,5-tetrahydrobenz[*cd*]indol-4-amines **1** have been found to be very potent serotonin and dopamine receptor agonists.[1] This series of ergoline partial structures resulted from extensive evaluations of structures that would mimic a locked-conformation analogue of serotonin itself. A variety of substituents have been installed in the 6-position (R = OCH_3, OH, $CONH_2$, H), in combination with the N.4 group (R' = alkyl).[2] Although the (racemic) synthesis of **1** has been accomplished by a variety of strategies,[1-4] it was desirable to have ready access to either antipode of **1** in order to facilitate the search for new members of this interesting class of compounds. Furthermore, **3** possesses the requisite stereochemistry at C.4 for the ergot alkaloids and other naturally occurring indoles, and could serve as an intermediate for natural product synthesis. It was therefore felt that the primary amines **2** and **3** would be key intermediates for syntheses of pure antipodes of **1**. We report here the first syntheses of these compounds.



1 **2** **3** **4**

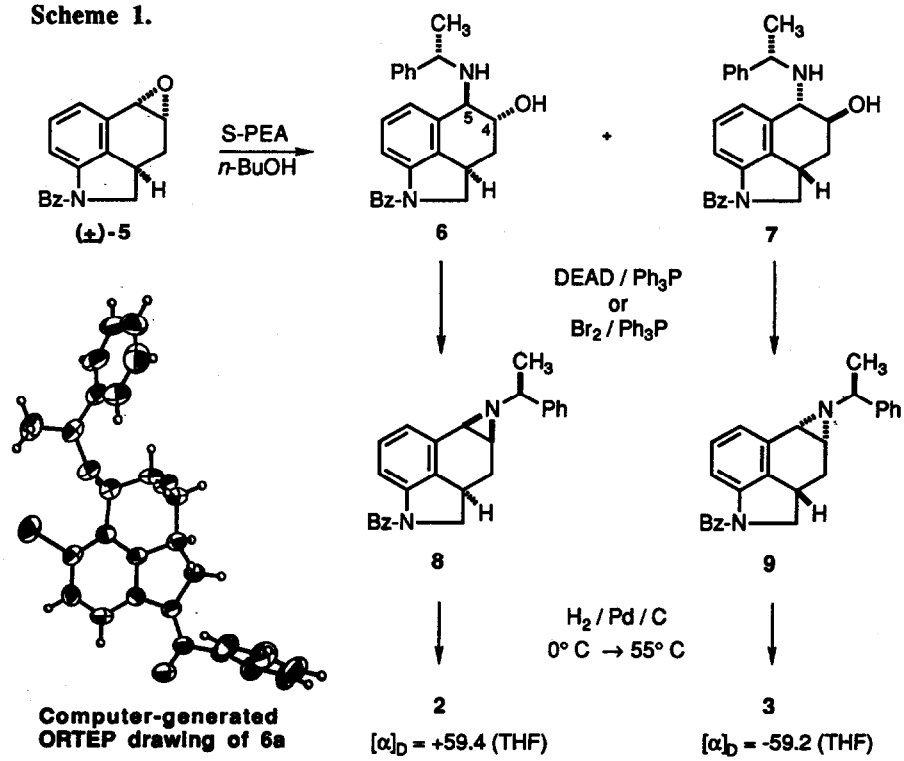
(Bz = PhCO)

We have previously reported on the diastereoselective epoxidation of **4** to afford the racemic epoxide **5**, with > 98% selectivity in excellent yield.[5] This selectivity was found to be quite general, in fact, for a variety of other polycyclic styrene derivatives.[6] On the basis of literature precedent,[4] we suspected epoxide **5** would undergo ring opening with amine nucleophiles to form the desired C.4-N bond. We found, however, that epoxide **5** reacted smoothly and regioselectively with S-phenylethylamine (S-PEA) in *n*-BuOH to afford amino alcohols **6** and **7** (Scheme 1). In fact, epoxide **5** reacted with a variety of amines ($R'NH_2$, R'_2NH) under neutral conditions[7] to yield identical regioselectivity. Amino alcohol **6** crystallized directly from the reaction mixture and was filtered to afford optically pure material, mp 192-193 °C (44% from **5**, de=99.5+%, HPLC, Scheme 1). X-ray analysis of **6a**, the corresponding 6-bromo derivative, confirmed the relative and absolute stereochemistry,[8] and is presented in Scheme 1.

The regiochemical outcome of the epoxide opening was disappointing in view of the reported opening in the Kornfeld-Woodward synthesis[4] of lysergic acid, where a sterically hindered benzylic C.5-substituted epoxide (cf. **5**) was employed which resulted in the opposite regiochemistry. We felt, however, that the nitrogen at C.5 could

be transposed around the *C*-ring through the intermediacy of aziridine **8** (and **9**), which was doubly benzylic in nature and subject to C-N bond hydrogenolysis. Thus, aziridine formation was accomplished under a variety of conditions, including Mitsunobu type and other activated triphenylphosphine reagents,[9a-c] or for example Et_3N-SO_3,[9d] to yield **8** as fine needles (*i*-PrOH), mp 184-186 °C, in 88% yield. The original amino alcohol mother liquor, comprised mainly of **7** and low levels of **6**, was also subjected to aziridine cyclization reaction, which after work-up and crystallization (*i*-PrOH) afforded diastereomerically pure **9** (38% from **5**, de=99+%, HPLC). It was interesting to note the empirical preference for amino alcohol **6** to crystallize from a mixture of **6** and **7**, whereas aziridine **9** crystallized from a mixture of **8** and **9**.

Scheme 1.

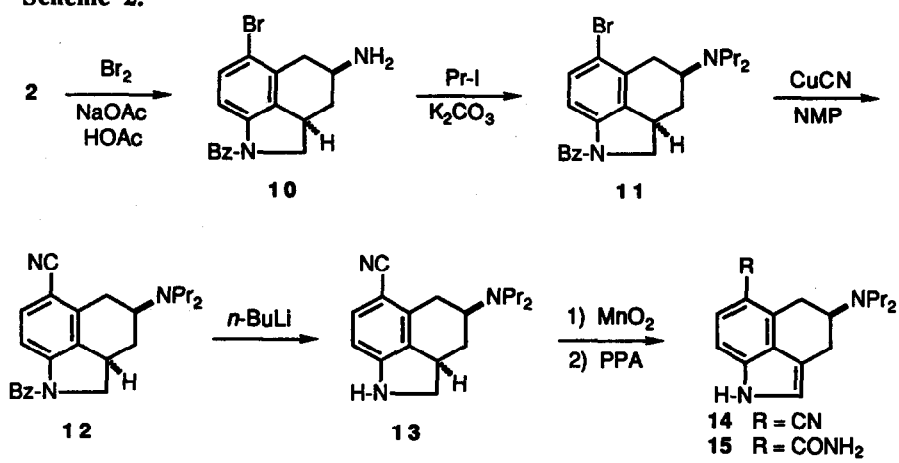


Catalytic hydrogenolysis[10] of **8** in glacial acetic acid with 10% Pd/C at 15 °C and 1 atm H_2 gave smooth cleavage of the aziridine ring N-C.5 bond, which could be easily followed by chromatographic analysis. Upon completion of the first hydrogenolysis, the second reduction occurred by stirring at 55 °C, with or without isolation of the intermediate secondary amine, to provide **2** ($[\alpha]_D$ = +59.4°, THF, *c*=1.00, Scheme 1). After filtration, removal of the volatiles and neutralization, recrystallization from 50% aqueous EtOH afforded **2** in 90% yield. The same tandem-hydrogenolysis reaction was applied to aziridine **9** to afford the enantiomeric primary amine **3**, with an equal but opposite rotation ($[\alpha]_D$ = -59.2°, THF, *c*=1.00, Scheme 1). The only detectable side-product from these reactions was the des-amino compound (i.e., loss of NH_2 from **2**, or **3**). Reduction of the aziridine **8** or **9** at elevated temperatures resulted in high levels (15-30%) of the des-amino compound.[11] This unwanted pathway could be minimized by careful temperature control, i.e., conduct the reductive ring opening at

low temperatures, followed by hydrogenolysis at elevated temperatures. The syntheses of optically pure primary amines **2** and **3** have thus been accomplished in three steps from readily available epoxide **5**.

The utility of primary amine **2** was highlighted by transformation to **15** (LY228729), an interesting serotonin receptor agonist.[1,2] Regioselective bromination[12] of **2** was accomplished directly in glacial acetic acid with NaOAc and bromine (2 eq) at room temperature without protection of the primary amine in 89% yield (Scheme 2). Alkylation with iodopropane and K_2CO_3 in CH_3CN[13] at 80 °C afforded the tertiary amine **11**, mp 93 °C (80%, Scheme 2). Rosemund-von Braun reaction (CuCN, NMP, 200 °C)[14] gave the nitrile **12** (76%), which was subsequently deprotected with *n*-BuLi (1.6 eq) at low temperature in 95% yield. Alternative methods for removal of the benzoyl group were less selective and resulted in lower yields. The resulting indoline **13** was purified by acid extraction and organic wash to remove the neutral by-products. Oxidation of **13** to the indole **14** was then effected in glacial acetic acid with activated MnO_2 (2 mol eq)[15] at 10 °C in 83% yield. Finally, nitrile hydrolysis to the amide **15** was conducted in neat polyphosphoric acid (PPA)[16] at 90 °C in essentially quantitative yield. The material obtained by this synthetic route was identical in both chemical properties and biological activity compared with material previously reported.[1a,17] The bromide **6a** was debrominated (10% Pd/C, H_2) to provide **6**, and the successful conversion of amino alcohol **6** to **15** thereby establishes the absolute configuration (*R* at C.4) and rotation of this antipode ($[\alpha]_D = -104°$, THF).

Scheme 2.



In conclusion, we have utilized the previously established[5] diastereomeric epoxidation of tricyclic olefin **4** to prepare easily separable diastereomeric amino alcohols **6** and **7**. We have shown that these amino alcohols can serve as precursors to the optically pure building blocks **2** and **3**, for ergoline partial structure synthesis. Both of these primary amines, **2** and **3**, were independently transformed to the partial ergolines, **15** and its antipode, respectively.

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(11) The des-amino compound (**2**, NH_2=H) was not observed when a pure isolated sample of either regio-isomeric secondary amine was resubjected to the reaction conditions, thereby excluding an elimination-reduction pathway.

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(17) We thank Dr. M.E. Flaugh for supplying us with a sample of **14**, as well as the corresponding chemical and pharmacological data.

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