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# Indolyl Participation in the Mitsunobu Reaction: Retention of Stereochemistry

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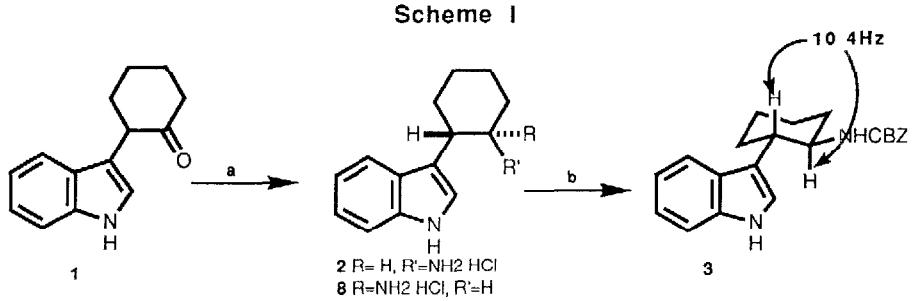
**Abstract:** The Mitsunobu reaction of *trans*-3-(2-hydroxycyclohexyl)indole with phthalimide results in the formation of *trans*-3-(2-N-phthalimidocyclohexyl)indole, presumably via indolyl participation in the displacement reaction. Involvement of symmetrical intermediate **7** is evidenced by deuterium label scrambling.

Recently Macor and Ryan described their efforts in the synthesis of 3-(2-aminocycloalkyl)methoxyindoles as conformationally restricted analogues of serotonin.[1] We, too, have been interested in the synthesis and the properties of (amino-cycloalkyl)indoles and the Pfizer report prompts us to disclose some related observations at this time.

Seeking stereoselective approaches to both the cis and trans amines (**2** & **8**), we envisaged the known 3-(-2-oxo-cyclohexyl)indole[2] ,**1**, as a potentially useful starting material for their preparation. Subjecting ketone **1** to reductive amination under the conditions of Danheiser et al ,afforded an 8:1 mixture of amines from which we obtained the pure trans amino indole **2** as a crystalline HCl salt.[3,4] Confirmation of the trans stereochemistry was achieved by NMR analysis of the corresponding CBZ derivative in which the diaxial coupling of 10 4 Hz was observed.[5]

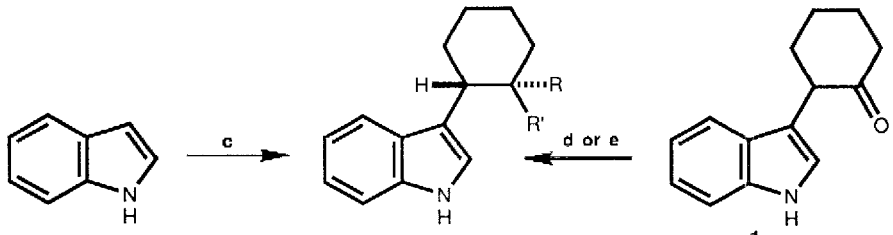
**Scheme I**




(**a** $NH_4OAc$, $NaBH_3CN$, iPrOH, 3Å sieves, RT , 72 hr; EtOAc, HCl, 76%yield. **b**· $NaHCO_3$ (aq.), benzyl chloroformate, $CH_2Cl_2$, 92% yield )

With a practical preparation of trans amine **2** in hand, we sought a stereoselective approach to the cis amine **6**. Our plans called for the utilization of trans alcohol **4** as a potential precursor to the cis amine via displacement (with inversion , in an $S_N2$ fashion) on an activated form of alcohol **4** with an appropriate nitrogen nucleophile. We envisaged the Mitsunobu protocol to be the most direct method by which to implement this transformation[8]. In turn, the trans alcohol was available by either of two routes. First, **4** could be stereoselectively prepared by reaction of indolylmagnesium bromide with cyclohexene oxide [1,6] Alternatively a mixture of the trans and cis alcohols **4** and **5** could be obtained by reduction of ketone **1** with a variety of hydride reducing agents The most selective of those tested was zinc borohydride ($NaBH_4$,1.5 1 trans·cis, 85% yield, $Zn(BH_4)_2$,4.2:1 trans·cis, 82% yield) [2,7] While the epoxide opening proved to be more efficient for preparation of quantities of alcohol **4**, the reduction of ketone **1** was useful in that it allowed preparation of significant quantities of cis alcohol (readily separable from the trans by silica gel chromatography) as well as specifically deuterated alcohol derivatives (vide infra)

**Scheme 2**

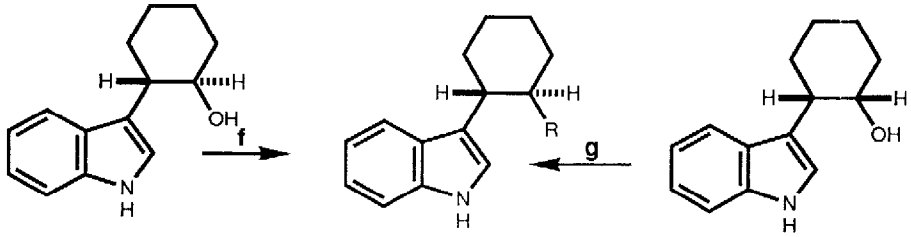



**4** R=H, R'=OH
**4D** R=D, R'=OH
**5** R=OH, R'=H
**5D** R=OH, R'=D

(**c**. EtMgBr, THF, cyclohexene oxide. **d**: $NaBH_4$, MeOH, 0°C,1.5·1 trans cis, or $Zn(BH_4)_2$, $Et_2O$, 4 2·1 trans·cis.**e**· $NaBD_4$, MeOH, 0°C, 1 5:1 trans cis )

We were gratified to discover that upon treatment of alcohol **4** under Mitsunobu conditions, a single phthalimido derivative **6** was isolated as the major product in 67% yield.[4,8] However, contrary to our hopes, the NMR data obtained was indicative of the trans stereochemistry (J = 10 4 Hz), suggesting retention of configuration in the Mitsunobu reaction! To confirm this stereochemical assignment, the phthalimide was cleaved (hydrazine, EtOH. reflux; EtOAc, HCl) to afford amine **2**, identical in all respects to that obtained via reductive amination (again analyzed as the CBZ derivative). Also noteworthy was the fact that the cis alcohol, when subjected to identical Mitsunobu reaction conditions, only sluggishly afforded the identical phthalimide in low yield (12% isolated yield, 55% recovered starting material).

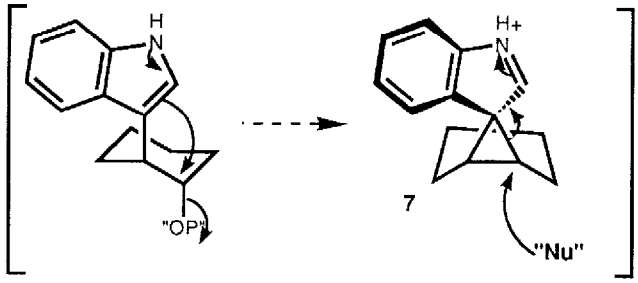
**Scheme 3**




(**f**: Ph3P, DEAD, THF, phthalimide, RT, 18hr, 87% yield. **g**· as in 3, 12% yield, 55% recovered SM )

To account for these observations, we propose participation (Scheme 4) on the part of the indole nucleus in the Mitsunobu reaction of trans alcohol **4**, leading ,via a symmetrical (meso) spirocyclopropan-iminium species such as **7**, to the trans phthalimido derivative, **6**.[9] The involvement of such intermediates has been well precedented in the chemistry of tryptophol and related derivatives[9] Geometric considerations prevent the cis alcohol from availing itself of this pathway and thus the Mitsunobu reaction proceeds via the expected $S_N2$ process (as evidenced by inversion of stereochemistry), again to provide trans phthalimide **6**, albeit in significantly lower yield.

**Scheme 4**




The consequences of the symmetry exhibited by structure **7** suggested an experimental rationale to validate its involvement in the Mitsunobu reaction Thus, the symmetry elements contained within intermediate 7 render the ring fusion carbons enantiotopic, and therefore chemically equivalent to an achiral nucleophile such as phthalimide [10] To probe the involvement of a species such as **7**, we prepared the deuterium labelled (at cyclohexyl C1) cis and trans alcohols (**4D** & **5D**) by $NaBD_4$ reduction of ketone **1**, and independently subjected each to

Mitsunobu reaction conditions as before. While the cis alcohol afforded phthalimide **6** maintaining deuterium label solely at cyclohexyl C1 (implicating a more traditional $S_N2$ process), the trans alcohol produced phthalimide **6** with scrambling of deuterium label to C1 and C2 (as an approximately 1:1 mixture), thus implicating the intermediacy of a symmetrical species such as **7**.[9,11] Further study of these systems and their application to the elucidation of the recognition requirements of neurotransmitter receptors is currently underway in our laboratories. The results of these investigations will be published in due course

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***References and Notes***

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9 For representative examples see· Ritchie, R , Sexton J.E. *J. Chem Res. (M)*, **1990**, 529-545, Ungemach, F , Cook, J M *Heterocycles*, **1978**, *9*, 1089-1119;Julia, M., Igolen, H., Lenzi, J *Bull Soc. Chem. France* **1966**, 2291; Clossen, W D , Roman, S.A , Kwiatkwoski, G.T , Corwin, D A *Tetrahedron Lett,* **1966**, 2271, Julia, M., Sliwa, H , Caubere, P. *Bull Soc. Chem. France* **1966**, 3359

10. An alternative method to implicate the intermediacy of a symmetrical species such as **7** would require preparation of enantiomerically enriched alcohol **4**, which upon reaction as above should lead to racemized phthalimide **6** if the reaction proceeded via a symmetrical intermediate

11 Our attempts to directly trap a spiro-cyclopropane species have thusfar been unsuccessful Treatment of ketone **2** with $B_2H_6$ (Cf Biswas, K M., Jackson, A H. *Tetrahedron*, **1969**, *25*, 227), upon referee's suggestion, afforded alcohols **4** and **5** as the only products detectable by capillary GC.

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