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NUCLEOPHILIC SUBSTITUTION REACTION IN INDOLE CHEMISTRY: A SYNTHESIS OF NOVEL 7β-SUBSTITUTED YOHIMBINE AND 4aα-SUBSTITUTED 1,2,3,4-TETRAHYDRO-β-CARBOLINE DERIVATIVES[1#]

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Abstract – X-Ray analyses of 1-hydroxyyohimbine derivatives clearly show the deviation of the N(1)—O bond from the indole molecular plane. This phenomenon supports our working hypothesis "bishomoallylic conjugation". The deviation is responsible for the unprecedented nucleophilic substitution reaction in 1-hydroxyindole chemistry and effected the synthesis of novel 7β-heteroarylyohimbine and 4aα-heteroaryl-1,2,3,4-tetrahydro-β-carboline derivatives from the corresponding 1-hydroxyindole derivatives.

We have disclosed that the unprecedented[2] nucleophilic substitution reaction in indole chemistry[3,4] takes place once a hydroxy group is introduced onto the nitrogen, N(1),[4,5] of the indole substrate. We can explain the reason based on our working hypothesis,[5] referred to as bishomoallylic conjugation.[5] Thus, the deviation angle θ of the N(1)—O bond (**A**, Scheme 1) from the indole molecular plane is responsible[4,5] for the nucleophilic substitution reactions of the 1-hydroxytryptamine and 1-hydroxytryptophan derivatives.[4,5] In this report, we now wish to describe further evidence for supporting the hypothesis by examining the reactions of 1-hydroxyyohimbine[6] (**1**) and 9-hydroxy-1,2,3,4-tetrahydro-β-carboline derivatives in the presence of a nucleophile.

Dedicated to the 70th birthday of Prof. Dr. Ryoji Noyori

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First, we prepared **1**,[6] 1-methoxyyohimbine (**2**),[6,7] and (*S*)-9-hydroxy-3β-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline[8] (**3**) according to our procedures.

Scheme 1

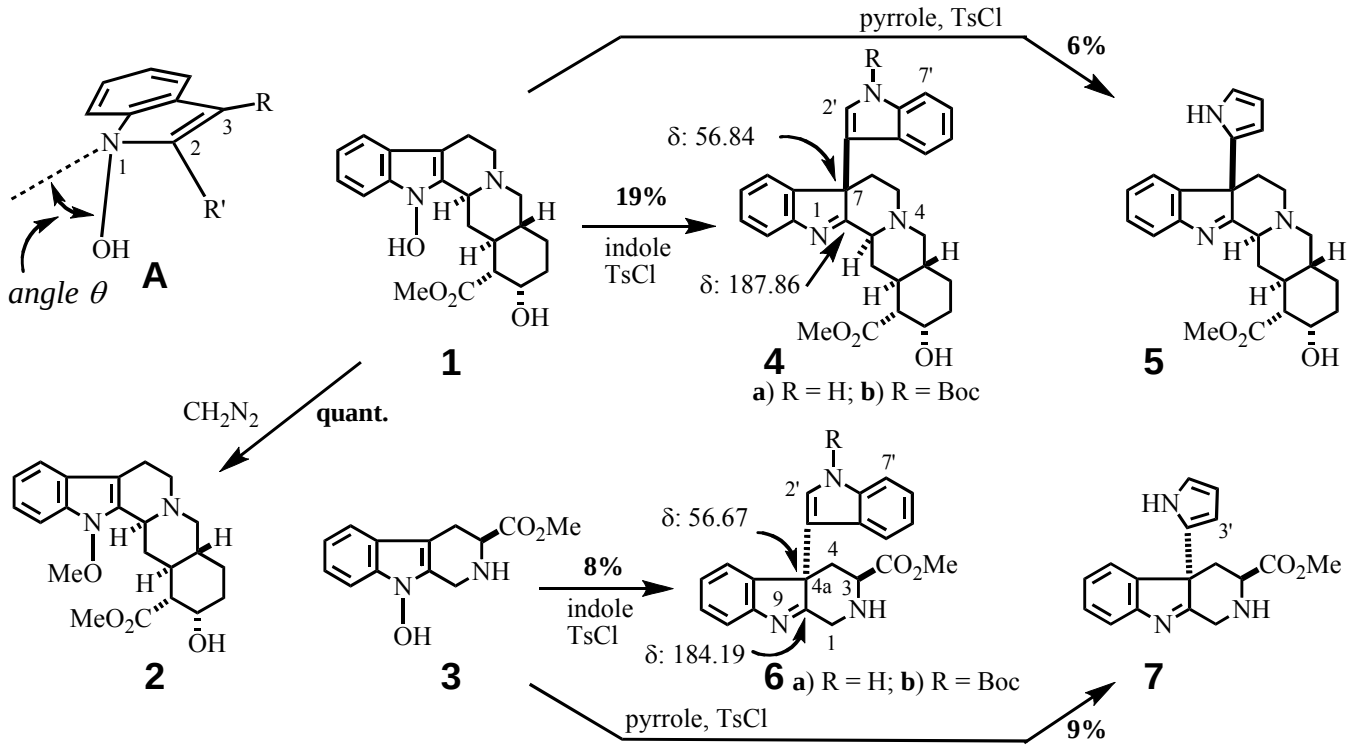


Figure 1

ORTEP Drawing of $\mathbf{1}H^{+}\cdot MeSO_3^{-}$ (*R* = 0.038)

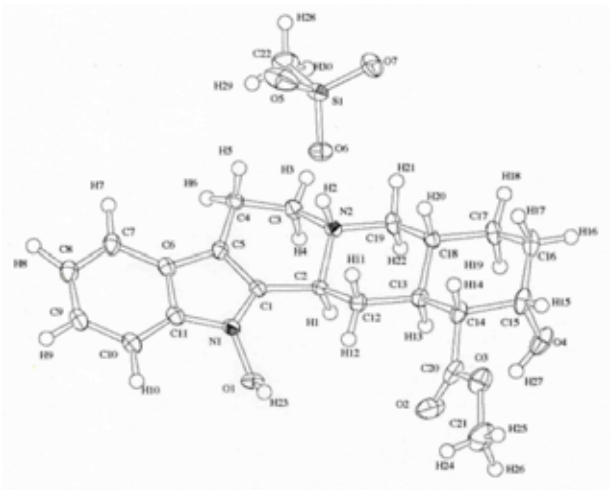
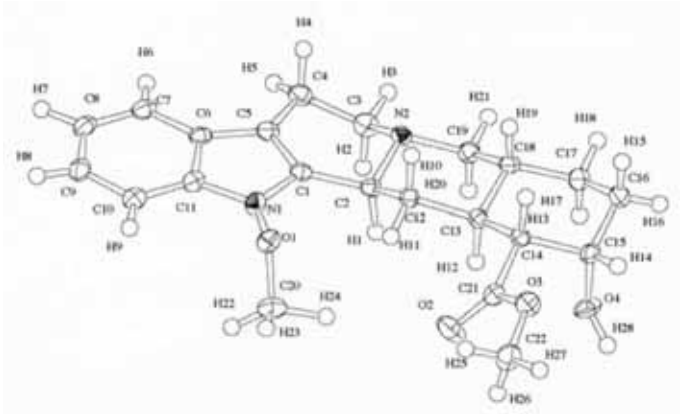
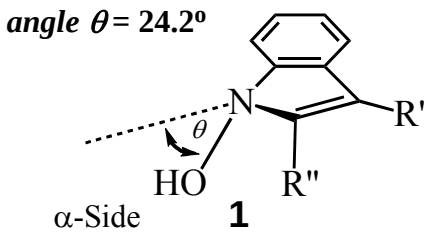
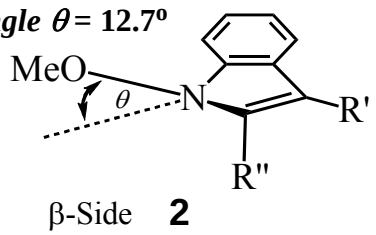


Figure 2

ORTEP Drawing of **2** (*R* = 0.035)







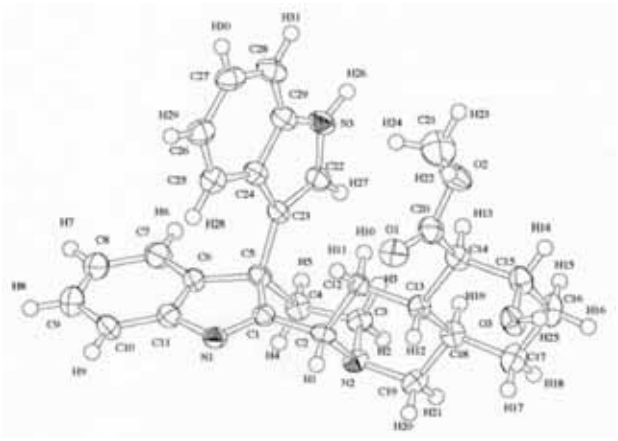
The ORTEP drawings[9] of X-ray single-crystal analysis for **1**$H^+ \cdot CH_3SO_3^-$ and **2** are shown in Figures 1 and 2, respectively. They clearly demonstrate that the N(1)—O bond in **1** and **2** have angle θs of 24.2° and 12.7°, respectively. These values are sufficient for expecting the nucleophilic substitution reactions to take place judged from our hypothesis.[5] It should be noted that the directions of the N(1)—O bond in **1** and **2** are opposite. Thus, the former is projecting below the molecular plane (α-side), while the latter above the plane (β-side) allowing the attached large methyl group to place in the less-hindered α-side. This means that the manipulation of the 1-hydroxy group of **1** inverts the initial stereochemistry of the N(1)—O bond.

With these data in consideration, **1** was reacted with tosyl chloride (TsCl) in $CHCl_3$-Et_3N at room temperature in the presence of indole. As expected, nucleophilic substitution reaction took place and among polymerized indole products, a 19% yield of **4a**[10a] was isolated as a major one. Elemental analysis and high-resolution mass spectrometry showed that an indole unit is introduced onto the yohimbine skeleton. Its ^{13}C-NMR spectrum showed characteristic signals at δ 187.86 and 56.84 ascribed to newly formed imine and quaternary carbons, C(2) and C(7), respectively.

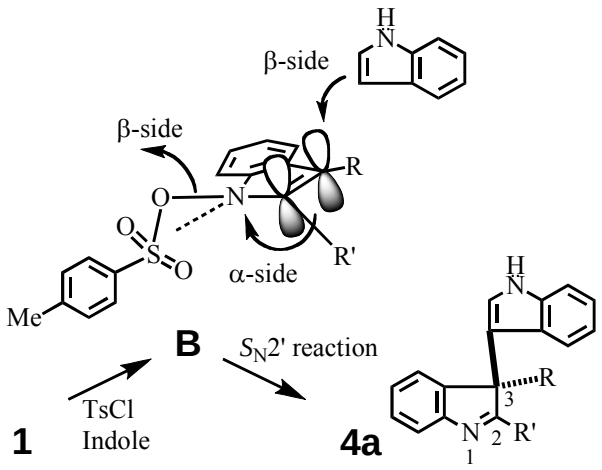
To get more information, **4a** was treated with Boc_2O to afford the 7β-(*N-tert*-butoxycarbonylindol-3-yl)-7*H*-yohimbine[10b] (**4b**) in 90% yield. Comparing the ^{1}H-NMR spectra of **4a** and **4b**, the Boc group is found to cause an anisotropic effect on both protons attached to the C(2') and C(7') suggesting that the introduced indole has a bond at the 3'-position. The X-ray single-crystal analysis of **4a** proved it to be 7β-(indol-3-yl)-7*H*-yohimbine as shown in ORTEP drawing in Figure 3. Similar reaction of **1** with TsCl in $CHCl_3$-Et_3N at room temperature in the presence of pyrrole afforded 6% yield of 7β-(pyrrol-2-yl)-7*H*-yohimbine[10c] (**5**) among polymers.

Figure 3

ORTEP Drawing of **4a** (R = 0.072)



Scheme 2

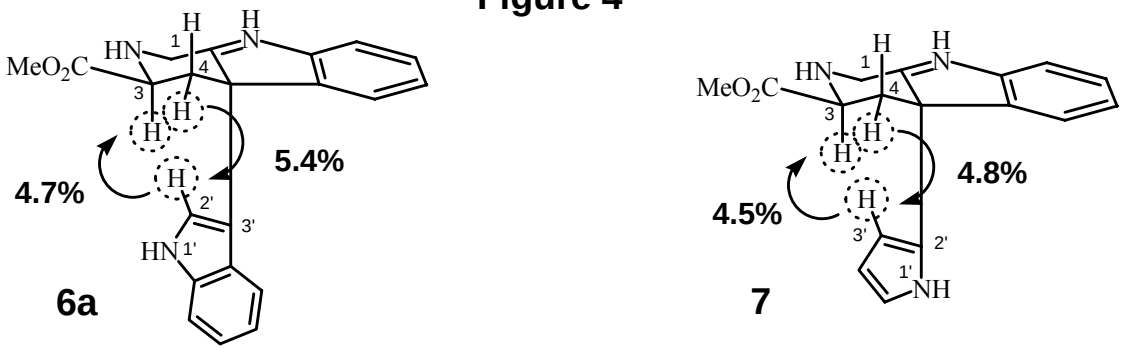


The stereoselective formation of **4a** could be explained by a concerted S_N2' mechanism as shown in Scheme 2. First, TsCl converts the 1-hydroxy to a good leaving 1-tosyloxy group. The direction of the N(1)—O bond projects to the β-side like **2**. On departure of the leaving group toward the β-side as shown in the transition state (**B**), indole π-electrons move and form the N(1)=C(2) double bond from the backside (α-side). Subsequent attack of the nucleophile (indole) at the C(3) from the β-side completes two sequential inversion steps to produce **4a**.

Similar nucleophilic substitution reactions were realized employing **3** as a starting material (Scheme 1). The reaction of **3** with TsCl in $CHCl_3$-Et_3N at room temperature in the presence of indole or pyrrole provided (*S*)-4aα-(indol-3-yl)-[10d] (**6a**) and (*S*)-4aα-(pyrrol-2-yl)-3β-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline[10e] (**7**) in 8 and 9% yields, respectively. The characteristic signals at δ 184.19 and 56.67 in the ^{13}C-NMR spectrum of **6a** showed newly formed imine and quaternary carbons, C(9a) and C(4a), respectively. Treatment of **6a** with Boc_2O in the presence of DMAP and Et_3N afforded (*S*)-4aα-(*N*-*tert*-butoxycarbonylindol-3-yl)-3β-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline[10f] (**6b**) in poor 9% yield probably because of steric crowding.

Since **6a**, **6b**, and **7** are all oily compounds, their stereochemistries are determined by nOe experiments. The results are shown in Figure 4. In the case of **6a**, nOe is observed between the proton pairs of H(2')—H(4, equatorial) and H(2')—H(3, axial) by 5.4 and 4.7%, respectively. In the case of **7**, nOe is observed between the pairs of H(3')—H(4, equatorial) and H(2')—H(3, axial) by 4.8 and 4.5%, respectively. Based on these data, their structures are proved as shown. These results suggested that selective introduction of nucleophiles occurred from the less hindered α-side of **3**.

Figure 4



In summary, we demonstrated examples of stereoselective nucleophilic substitution reactions based on 1-hydroxyindole chemistry and succeeded in the production of thus far unknown 7β-heteroarylyohimbine and 4aα-heteroaryl-1,2,3,4-tetrahydro-β-carboline derivatives. Although the yields of them are poor at present, further examination for establishing the optimal reaction conditions would overcome the problem. These novel compounds are expected to be a new family of biologically

active compounds.

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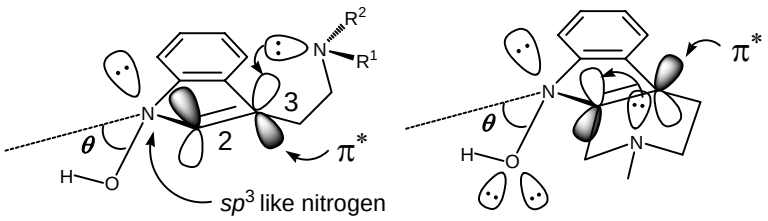
5. In the conformation as shown in Figure 5, the lone pair on a bishomoallylic *N*b-nitrogen could interact with π* orbital of the C(2)—C(3). The *N*b-nitrogen can lend a little electron density to the π* orbital weakening the C(2)—C(3) π-bond and making the original sp^2-N(1) partly free from the 10π-aromatic system. As a result the N(1) becomes sp^3 like, resulting in the deviation of the N(1)—O bond from the indole molecular plane. Thereby, the repulsions between the lone pairs of N(1) and those of

Figure 5
Bishomoallylic Conjugation



hydroxy oxygen become the least. Now the 6π-electrons of the isolated benzene can interact with the developing positive-charge of the sp^3 nitrogen on the departure of the hydroxy group. Consequently nucleophilic substitution reaction at the 5- and/or other positions of indole nucleus becomes possible. For more details: M. Somei, "Topics in Heterocyclic Chemistry", Vol. 6, ed. by S. Eguchi, Springer-Verlag, Berlin, 2006, pp. 77—111.

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8. Mp 185—187°C (colorless fine needles, recrystallized from MeOH–$CHCl_3$–hexane): K. Noguchi, Master Thesis, Kanazawa University, 2000, March.
9. All measurements were made on a Rigaku/MSC Mercury diffract meter with graphite monochromated Mo-Kα radiation. All calculations were performed using the teXsan package.[11] The structure was solved by a direct method (SIR).[12] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. Detailed crystal data would be reported elsewhere in due course.
10. a) mp 167—169°C (decomp., colorless prisms, recrystallized from MeOH). b) pale yellow oil. c) pale yellow oil. d) pale yellow oil. e) pale yellow oil. f) pale yellow oil.
11. teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation, 1985 & 1999.
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