INOC REACTION IN ALKALOID SYNTHESIS— PREPARATION OF POTENTIAL INTERMEDIATE FOR THE SYNTHESIS OF (-)-RESERPINE—

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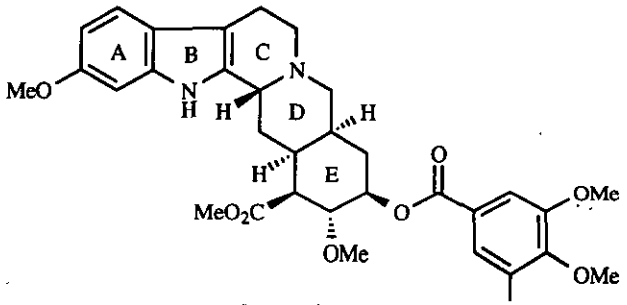
Abstract——Intramolecular nitrile oxide cycloaddition (INOC) reaction of the nitro olefin (**10**) furnished the isoxazoline (**11**), potential synthon for the E ring segment of (-)-reserpine (**1**), in quantitative yield.

Owing to its roles both as target for natural product synthetic adventure and as medicinal agent in the treatment of hypertension and mental disorders,[1] reserpine (**1**)[2] has attracted wide interest. The first synthesis of **1** was reported by Woodward and his colleagues in 1956.[3a] After considerable efforts, 5 total syntheses[3] have been reported to date.



Reserpine (**1**)

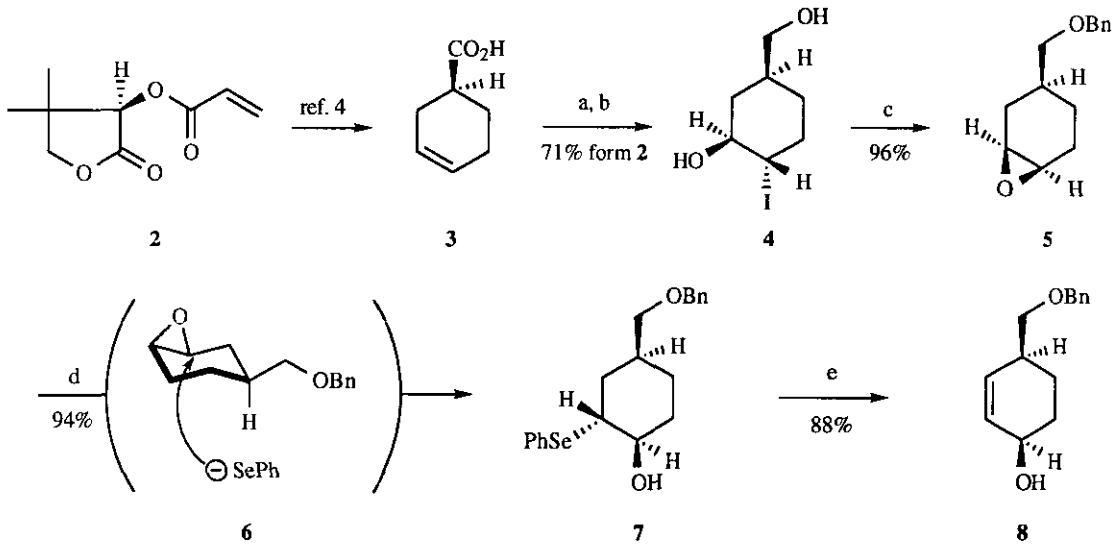
A central issue addressed differently in the above-mentioned approaches to reserpine (**1**) is found in the construction of its stereochemically complex E ring system. We herein disclose our investigation including the preparation of an enantiomerically pure desirable precursor for the E ring part of (-)-reserpine (**1**) *via* INOC reaction.

First of all, the readily available optically pure 3-cyclohexenecarboxylic acid (**3**), prepared from acrylate (**2**) by using Helmchen's protocol,[4] was transformed into the allylic alcohol (**8**), as shown in Scheme I. Namely, treatment of **3** with iodine and potassium iodide in the presence of sodium hydrogen carbonate afforded the corresponding iodolactone, which was subjected to DIBAH reduction at -78 °C, giving the diol (**4**) in 71% yield from **2**. After basic treatment of **4** with sodium hydride in DMF followed by benzylation, the epoxide (**5**) (96% from **4**) was obtained.

Conformational effects which favor *trans* diaxial ring opening reaction are well established in the reactions of 6-membered ring epoxides. The selenium anion then approached form α-side which, according to Fürst-Plattner

rule,[5] gave rise to the diaxial product (**7**) in 94% yield. The hydroxy selenide was next oxidized by excess 30% hydrogen peroxide to the unstable selenoxide, which was transformed to the allylic alcohol (**8**) (88%).

Scheme I



Reagents and conditions: a, I_2, KI, $NaHCO_3$, CH_2Cl_2-H_2O (1 : 1 v/v), 0 °C, b, DIBAH, THF, -78 °C, c, 60% NaH, DMF; BnBr, 0 °C → room temperature, d, PhSeNa, EtOH, e, 30% H_2O_2, THF, 0 °C → room temperature,; THF, reflux.

The preparation of isoxazoline (**11**) from **8** is summarized in Scheme II. Vinyletherification of **8** proved to be problematic until recourse was made to catalysis by mercuric trifluoroacetate in the presence of triethylamine. Under these conditions, the corresponding vinyl enol ether was obtained in 79% yield. Thermal Claisen rearrangement of the above vinyl ether was conducted at 180 °C for 17 h to furnish the aldehyde (**9**) (89%). Chain extension was next accomplished by sequential Henry reaction ($MeNO_2$, KF, $^nBu_4NCl$, toluene, room temperature, 99%), acetylation (Ac_2O, pyridine) and reduction with $NaBH_4$ in EtOH (84% yield from nitro aldol).

With the efficient synthesis of nitro olefin (**10**)[6] realized, the stage was now set for INOC reaction.[7] The compound (**10**) was reacted with excess *p*-chlorophenyl isocyanate in the presence of triethylamine at 60 °C. The transient nitrite oxide was intercepted by the tethered olefin to deliver a single isoxazoline (**11**)[6] in quantitative yield. The stereochemistry of **11** was made clearly apparent through combined 2-D COSY study and NOE measurements. The relevant NOE data for **11** were presented by arrows in Figure I.

Finally, the isoxazoline (**11**) was transformed into the β-hydroxy ketone (**12**) by hydrogenation over freshly prepared W-2 Raney nickel in a 15 : 1 mixture of methanol and water containing 10 equivalent of trimethoxyborane.[8]

Scheme II

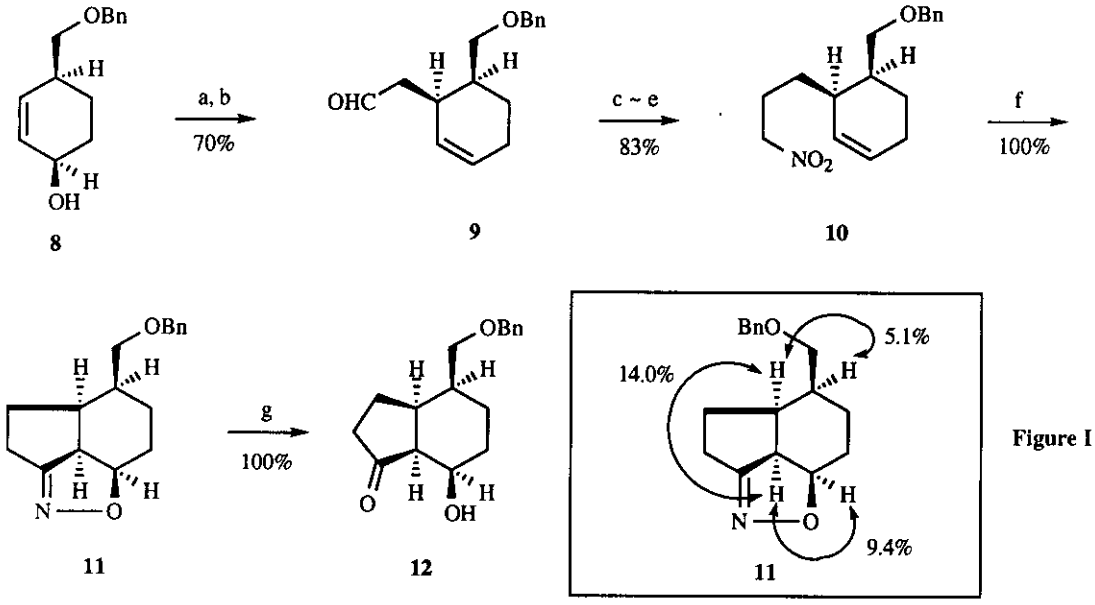


Figure I

Reagents and conditions: a, CH_2=CHOEt, $Hg(OCOCF_3)_2$, Et_3N, b, 180 °C, toluene, sealed tube, 17 h, c, $MeNO_2$, KF, $^nBu_4NCl$, toluene, d, Ac_2O, Py, e, $NaBH_4$, EtOH, 0 °C, f, *p*-ClC_6H_4N=C=O, Et_3N, toluene, 60 °C, g, H_2, Raney Ni(W2), $(MeO)_3B$, MeOH-H_2O (15 : 1 v/v).

Further studies toward this direction are currently underway.

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6. Satisfactory analytical data were obtained for all new compounds. Selected data are as follows. *Compound* (**10**); $[\alpha]_D^{20}$ -111.64 ° (c 1.72, $CHCl_3$); ir ν_{max} (neat): 1560 cm^{-1}; ^1H nmr ($CDCl_3$): δ 3.31-3.44 (2H, m), 4.33 (2H, t, *J* = 7.0 Hz), 4.49 (2H, dd, *J* = 12.0 and 15.0 Hz), and 5.60-5.74 (2H, m). *Compound* (**11**);

$[\alpha]_D^{23}$ -99.29 ° (c 2.61, $CHCl_3$); ^1H nmr ($CDCl_3$): δ 3.31 (2H, br d, J = 7.5 Hz), 3.79 (1H, t, J = 11.5 Hz), 4.48 (2H, dd, J = 12.0 and 15.0 Hz), and 4.75 (1H, br ddd, J = 1.0, 6.0, and 11.0 Hz).

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