

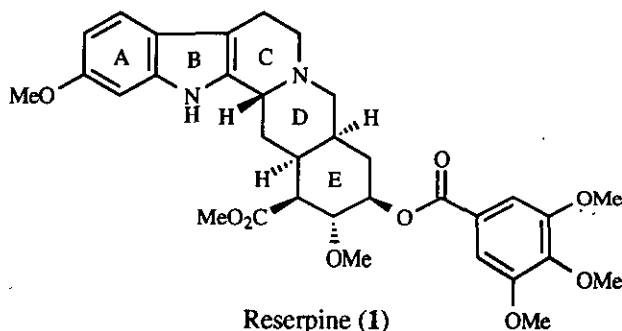
## INOC REACTION IN ALKALOID SYNTHESIS— PREPARATION OF POTENTIAL INTERMEDIATE FOR THE SYNTHESIS OF (-)-RESERPINE—

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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,<sup>1</sup> reserpine (**1**)<sup>2</sup> has attracted wide interest. The first synthesis of **1** was reported by Woodward and his colleagues in 1956.<sup>3a</sup> After considerable efforts, 5 total syntheses<sup>3</sup> have been reported to date.



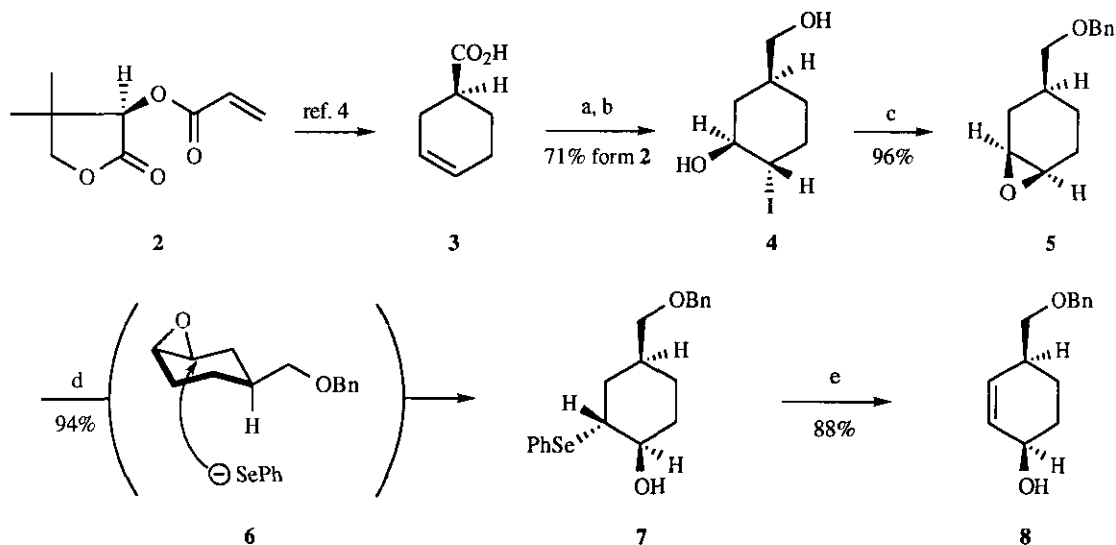
A central issue addressed differently in the above-mentioned approaches to reserpine (**1**) is found in the construction of its stereochemically complex E ring system. We herein disclose our investigation including the preparation of an enantiomerically pure desirable precursor for the E ring part of (-)-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,<sup>4</sup> 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 from  $\alpha$ -side which, according to Fürst-Plattner

rule,<sup>5</sup> 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



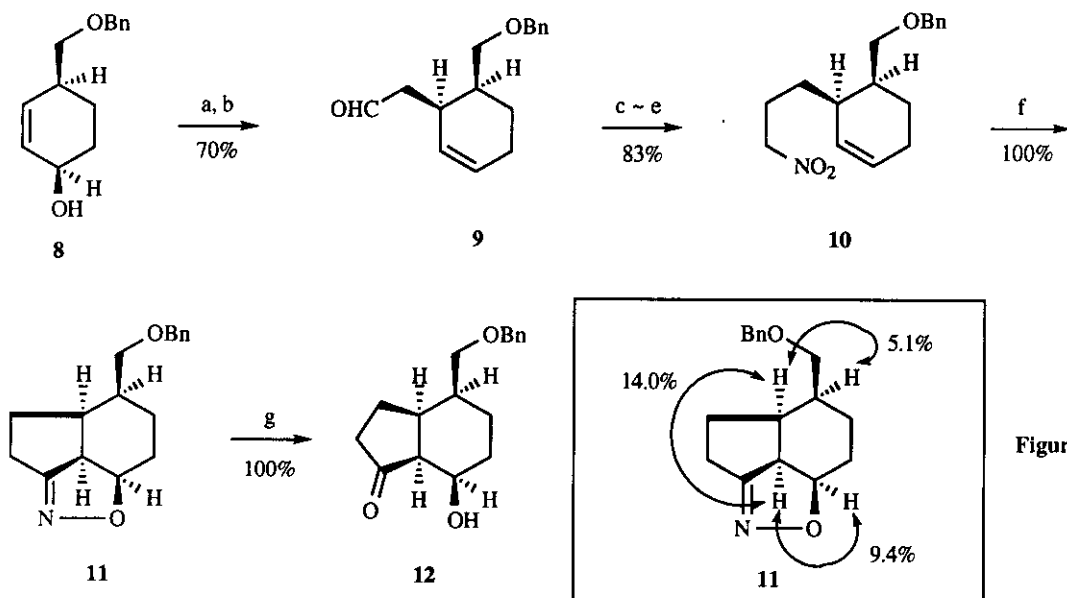
**Reagents and conditions:** a,  $\text{I}_2$ , KI,  $\text{NaHCO}_3$ ,  $\text{CH}_2\text{Cl}_2$ - $\text{H}_2\text{O}$  (1 : 1 v/v),  $0^\circ\text{C}$ , b, DIBALH, THF,  $-78^\circ\text{C}$ , c, 60% NaH, DMF; BnBr,  $0^\circ\text{C} \rightarrow$  room temperature, d, PhSeNa, EtOH, e, 30%  $\text{H}_2\text{O}_2$ , THF,  $0^\circ\text{C} \rightarrow$  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  $180^\circ\text{C}$  for 17 h to furnish the aldehyde (**9**) (89%). Chain extension was next accomplished by sequential Henry reaction ( $\text{MeNO}_2$ , KF,  ${}^n\text{Bu}_4\text{NCl}$ , toluene, room temperature, 99%), acetylation ( $\text{Ac}_2\text{O}$ , pyridine) and reduction with  $\text{NaBH}_4$  in EtOH (84% yield from nitro aldol).

With the efficient synthesis of nitro olefin (**10**)<sup>6</sup> realized, the stage was now set for INOC reaction.<sup>7</sup> The compound (**10**) was reacted with excess *p*-chlorophenyl isocyanate in the presence of triethylamine at  $60^\circ\text{C}$ . The transient nitrite oxide was intercepted by the tethered olefin to deliver a single isoxazoline (**11**)<sup>6</sup> 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  $\beta$ -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.<sup>8</sup>

Scheme II



**Reagents and conditions:** a,  $\text{CH}_2=\text{CHOEt}$ ,  $\text{Hg}(\text{OCOFC}_3)_2$ ,  $\text{Et}_3\text{N}$ , b,  $180^\circ\text{C}$ , toluene, sealed tube, 17 h, c,  $\text{MeNO}_2$ ,  $\text{KF}$ ,  $^n\text{Bu}_4\text{NCl}$ , toluene, d,  $\text{Ac}_2\text{O}$ ,  $\text{Py}$ , e,  $\text{NaBH}_4$ ,  $\text{EtOH}$ ,  $0^\circ\text{C}$ , f,  $p\text{-ClC}_6\text{H}_4\text{N}=\text{C}=\text{O}$ ,  $\text{Et}_3\text{N}$ , toluene,  $60^\circ\text{C}$ , g,  $\text{H}_2$ , Raney  $\text{Ni}(\text{W}2)$ ,  $(\text{MeO})_3\text{B}$ ,  $\text{MeOH}-\text{H}_2\text{O}$  (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)*;  $[\alpha]_{\text{D}}^{20} -111.64^\circ$  (c 1.72,  $\text{CHCl}_3$ );  $\text{ir } \nu_{\text{max}}$  (neat):  $1560\text{ cm}^{-1}$ ;  $^1\text{H nmr}$  ( $\text{CDCl}_3$ ):  $\delta$  3.31-3.44 (2H, m), 4.33 (2H, t,  $J = 7.0\text{ Hz}$ ), 4.49 (2H, dd,  $J = 12.0$  and  $15.0\text{ Hz}$ ), and 5.60-5.74 (2H, m). *Compound (11)*;

$[\alpha]_{\text{D}}^{23} -99.29^\circ$  (c 2.61,  $\text{CHCl}_3$ );  $^1\text{H}$  nmr ( $\text{CDCl}_3$ ):  $\delta$  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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Received, 20th December, 1994