

# $\alpha,\beta$ - UNSATURATED LACTONE-NITRONE CYCLOADDITIONS. A ROUTE TO THE SYNTHESIS OF ( $\pm$ ) -TUSSILAGIN

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## ملخص

لقد أدى تفاعل النيترون (5) مع مركب اللاكتون الغير مشبع (6) الى فصل ناتج واحد فقط (7). ان السيطرة الربيوكيميائية العالية في هذه التفاعلات شجعت على اعطاء دفعة قوية في كشف جديد لتحضير النواتج الطبيعية. ان هذا البحث يتضمن وصف كامل لطريقة جديدة مؤدية الى تحضير الناتج الطبيعي : توسيلاجين.

## ABSTRACT

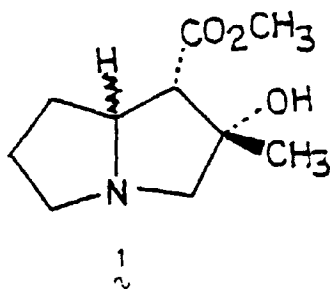
Reaction of nitrone (5) with  $\alpha,\beta$ -unsaturated lactone (6) resulted in the isolation of a single adduct (7). The observed high regiochemical control has encouraged further explorations of natural product synthesis. A route to the synthesis of an interesting member of Pyrrolizidine-Alkaloid family; ( $\pm$ )-Tussilagin (1), has been described

## INTRODUCTION

The development of the chemistry of 1,3- dipolar cycloaddition reactions of nitrones,<sup>[1,2]</sup> which began in the late fifties,<sup>[3]</sup> has recently had a significant impact on the synthesis of natural products.<sup>[4]</sup> Several recent studies have emphasized the use of nitrones in the synthesis of alkaloidal systems.<sup>[5-8]</sup>

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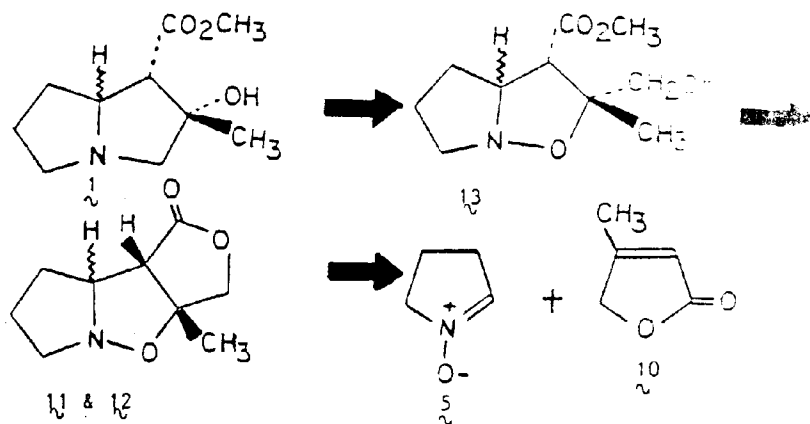
The additions of nitrones to a wide variety of dipolarophiles have been shown to have a high regiochemical control.<sup>[9]</sup> In the present research, the cycloaddition reaction of a five membered ring nitronc onto  $\alpha,\beta$  -unsaturated lactone has shown to have a very high regiochemical control. It would seem likely that the presence of strongly attracting groups on the dipolarophile tends to favor a transition state where carbon-oxygen bond formation leads (Michael - like character).<sup>[10]</sup> The observed results have encouraged us to utilize a synthetic route to the synthesis of an elegant natural product; ( $\pm$ ) -Tussilagin 1. Tussilagin is a naturally occurring compound which has antitumor properties. It is a member of Pyrrolizidine-Alkaloids family.<sup>[11,12]</sup> The structure of Tussilagin has been confirmed by x-ray crystallography and other methods of analysis.<sup>[11,12]</sup>



## RESULTS AND DISCUSSION

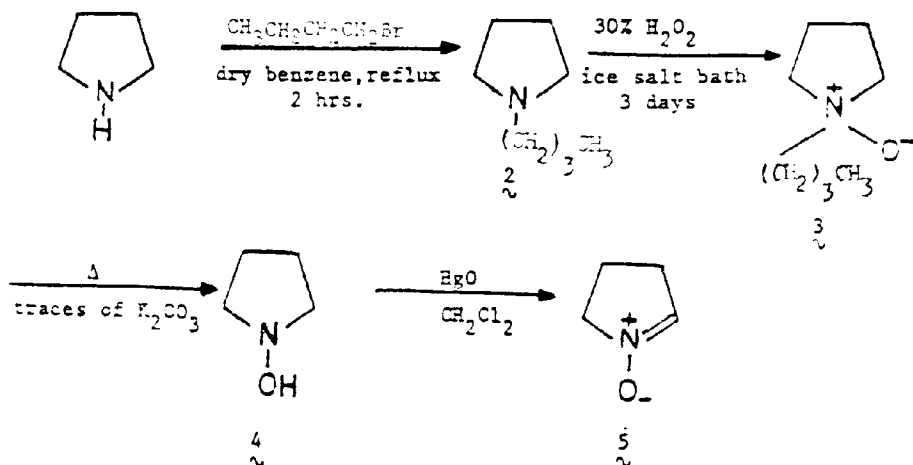
The retrosynthetic scheme led us to consider a 1,3-dipolar nitronc cycloaddition reaction using an unsaturated lactone as a new dipolarophile (Scheme I).

# Scheme (I)



The nitron, 1-pyrroline -1- oxide 5, was prepared in a four-step route as shown in Scheme II.

# Scheme (II)

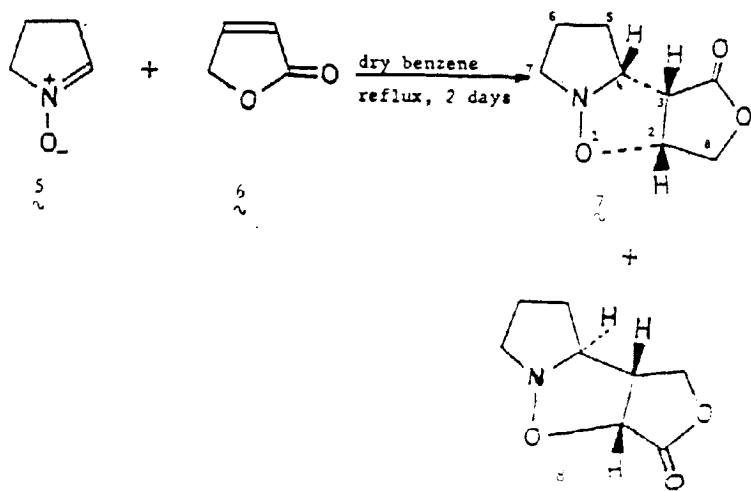


The reaction of pyrrolidine with n-butyl bromide was carried out under reflux for 2 hours in dry benzene to afford n-butylpyrrolidine

2 in 85% yield as a colorless liquid.<sup>[13]</sup> Oxidation of compound 2 with a 30% aqueous hydrogen peroxide solution at room temperature for 3 days afforded the oxide 3 in 75% yield as a light yellow viscous oil. The nmr spectrum was difficult to interpret, as most of the signals are multiplets. The Cope reaction of oxide 3 afforded N-hydroxypyrrolidine 4 in 80% yield. The nmr spectrum exhibited a complex pattern at  $\delta$ 1.43 for the C-3 and the C-4 protons, a multiplet at  $\delta$ 3.10 for the C-2 and the C-5 protons. The deuterium exchangeable OH proton appeared at  $\delta$ 8.15. Nitron 5 was prepared by a mercuric oxide oxidation<sup>[14]</sup> of the hydroxylamine 4. The nmr spectrum disclosed a multiplet at  $\delta$ 1.92 for the C-3 and the C-4 protons, a complex pattern at  $\delta$ 3.90 for the C-5 protons and a complex pattern at  $\delta$ 6.95 for the C-2 proton.

The cycloaddition reaction of nitron 5 with  $\alpha,\beta$ -unsaturated lactone 6 is shown in Scheme III.

Scheme (III)

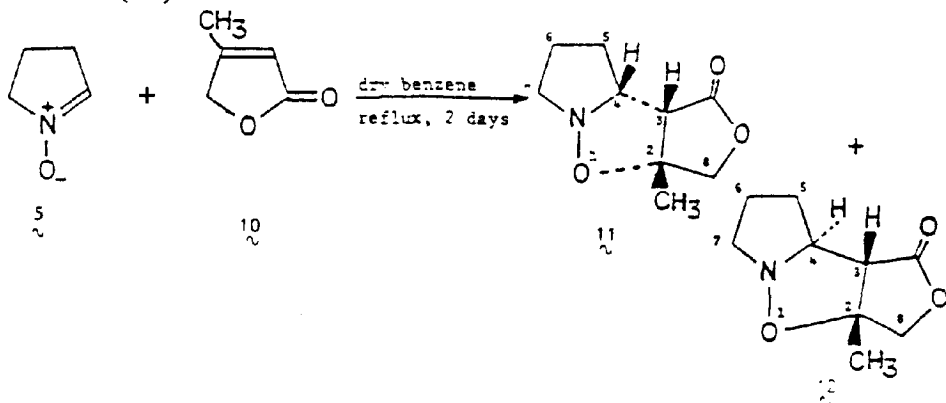


A single adduct **7** has only been isolated. On the basis of a spin decoupling experiment, it has been confirmed that no traces of adduct **8** has been detected.<sup>[19]</sup>

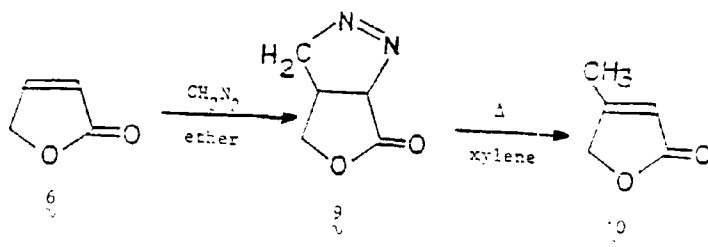
Isoxazolidine **7** (MS:  $M^+$  169) shows lactone carbonyl absorption in the region of 5.55 - 5.90  $\mu$  of the infrared. The NMR spectrum ( $CDCl_3$ , 250 MHz) shows a complex pattern at  $\delta$  1.75 for the C-5 protons, a complex pattern at  $\delta$  2.1 for the C-6 protons, a multiplet at  $\delta$  3.1 for the C-3 proton, a multiplet at  $\delta$  3.5 for the C-7 protons, a triplet at  $\delta$  3.5 for the C-7 protons, a triplet at  $\delta$  3.9 (t, 1,  $J = 2.0$  Hz) for the C-4 proton, a complex pattern at  $\delta$  4.45 for the C-8 protons, and a complex pattern at  $\delta$  4.93 for the C-2 proton.

It would seem likely that the presence of strongly attracting groups on the dipolarophile tends to favor a transition state where carbon - oxygen bond formation leads (Michael - like character).<sup>[10]</sup> The high regiochemical control in this type of cycloaddition has prompted us to utilize a synthetic route as an approach to the synthesis of ( $\pm$ )-Tussilagin **1**. The cycloaddition reaction of nitron **5** with unsaturated lactone **10** is shown in Scheme IV.

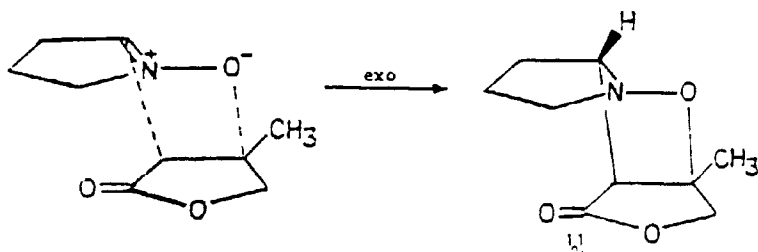
Scheme (IV)



## Scheme (V)



The Cycloaddition of a benzene solution of nitronc 5 and 4-methyl-2(5H)-furanone 10<sup>[15]</sup> (Scheme V) at 100° for 2 days furnished a mixture of stereoisomers in 70% yield. The mixture, which contains *exo/endo* isomers in a ratio of 75/25 corresponds to *exo*- and *endo*-isoxazolidines, 11 and 12 respectively. As anticipated,<sup>[16,17]</sup> alkene - nitronc cycloadditions proceed via exo-transition state predominantly.



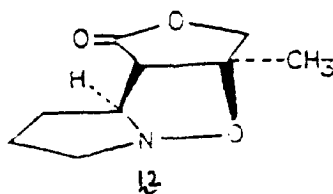
The mixture of stereoisomers was separated using column chromatography (silica gel, 7:3 (v/v) methylene chloride/ ethyl acetate).

Isoxazolidine  $\underset{\sim}{11}$  (MS:M' 183) shows lactone carbonyl absorption in the  $5.56 - 5.80\mu$  region of the infrared. The NMR spectrum ( $\text{CDCl}_3$ , 250 MHz) shows a singlet at  $\delta 1.52$  for the methyl protons, a complex pattern at  $\delta 1.75$  for the C-5 protons, a complex pattern at  $\delta 2.15$  for the C-6 protons, a multiplet at  $\delta 3.0$  for the C-3 proton and for  $\text{H}_\beta$  of the C-7, a multiplet at  $\delta 3.42$  for the  $\text{H}_\alpha$  of the C-7, a triplet at  $\delta 3.73$  (t,1,J = 2.5 Hz) for the C-4 proton, a doublet at  $\delta 4.15$  (d,1,J = 3.0 Hz) for  $\text{H}_\alpha$  of the C-8.

Isoxazolidine  $\underset{\sim}{12}$  (MS:M' 183) shows lactone carbonyl absorption in the region of  $5.60 - 5.85\mu$  region of the infrared. The NMR spectrum ( $\text{CDCl}_3$ , 250 MHz) shows a singlet at  $\delta 1.58$  for methyl protons, a complex pattern at  $\delta 1.95$  for the C-5 and the C-6 protons, a multiplet at  $\delta 2.97$  for the C-3 proton, a multiplet at  $\delta 3.3$  for the C-7 protons, a multiplet at  $\delta 4.0$  for the C-7 protons, a multiplet at  $\delta 4.0$  for the C-4 proton, a doublet at  $\delta 4.08$  (d,1,J=2.5 Hz) for the  $\text{H}_\beta$  of the C-8, and a doublet at  $\delta 4.32$  (d,1,J=2.5 Hz) for the  $\text{H}_\alpha$  of the C-8.

The orientation of cis-isomer  $\underset{\sim}{11}$  and trans-isomer  $\underset{\sim}{12}$  was assigned on the basis of a spin decoupling experiments.

The structural models of isomers  $\underset{\sim}{11}$  and  $\underset{\sim}{12}$  show that structure  $\underset{\sim}{11}$  is less hindered than structure  $\underset{\sim}{12}$ .



Few steps toward the target molecule; ( $\pm$ )-Tussilagin 1, are being executed and will be reported in the next paper.

## EXPERIMENTAL

The melting points, determined on a Mel-Temp capillary tube apparatus and boiling points, are reported in °C (uncorrected).

Infrared spectra (ir) have been determined on a Perkin - Elmer 1310 spectrometer and calibrated using the  $6.238\mu$  band of polystyrene; infrared data are reported in microns, where w,m , and s indicate the intensity of absorption as weak, medium, and strong respectively. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker EM 250 (250 MHz) spectrometer using tetramethylsilane as an internal standard . Chemical shifts data are reported in parts per million (ppm) downfield from tetramethylsilane using the delta ( $\delta$ ) scale. Coupling constants (J) are given in hertz (Hz). Splitting patterns are designated s,d,dd,t,q, quint,m,and cp designate singlet, doublet, doublet of doublets, triplet, quartet, quintet, multiplet, and complex pattern, respectively. The integration numbers are shown in parentheses. Mass spectra were recorded on a Hitachi Perkin - Elmer RMU- 6E spectrometer with an ionization voltage of 70 volts and a current of  $80\mu\text{A}$ .

### 1-Pyrroline 1-oxide (5)

Using the modified procedure of Thesing and Sirrenberg,<sup>[14]</sup> compound 5 was prepared. To a vigorously stirred solution of N-hydroxyamine 4 [1.0 g, 11.0 mmol] in chloroform (100 ml) at 0°C was added yellow mercuric oxide (6.20g, 29 mmol). After stirring for two



hours , several spatulas full of anhydrous magnesium sulfate were added to the dark green suspension and stirring was continued for another hour. The cold suspension was filtered through a magnesium sulfate pad and the filtrate solution was used in subsequent reactions. Solvent removal in vacuo gave a light yellow oil (0.90 g, 92%) IR (neat) 3.23 (s), 3.38 (m), 6.33 (s), 6.90(m), 7.33(m), 8.19 (s), 8.61(w), 9.61 (m), 9.96 (m), 10.70(m), 12.80 (m), 14.50 (m), and 16.02 (m) $\mu$ ;  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  1.60 - 2.90 (cp, 2H), 2.05 - 2.29 (cp, 2H) 2.90-3.1 (cp, 2H), and  $\delta$  6.94 (cp, 1H).

#### 4-Methyl -2(5H)- furanone (10):

The procedure of Pelletier<sup>[15]</sup> was modified and used to prepare compound 10. The ethereal solution of diazomethane (2.50g, 60 mmol) was added slowly to a stirred solution of the 2(5H)-furanone <sup>[18,19]</sup> (3.50g, 40 mmol) in THF at room temperature for a period of 15 - 30 min, and stirred at the same temperature for 1-8 hour. The crystalline adduct 10 was collected, yield (3.50g, 75%), m.p. 109 - 110°C, and the filtrate evaporated under reduced pressure. Compound 10 (2.50 g) in dioxane (25 ml) was heated in an oil bath at 120°C with stirring for 48 hours. After removal of solvent with a rotary evaporator, the yellow oil remaining was distilled to yield 1.5g (77%) of 10. Compound 10 showed: b.p. 112 - 113°/14 mm Hg; IR(neat): 5.60 (s), 5.62 (s), and 6.06(s) $\mu$ ;  $^1\text{H}$  NMR(250 MHz,  $\text{CDCl}_3$ ),  $\delta$  2.15 (s, 3H), 4.62 (s, 2H), and  $\delta$  5.83 (m, 1H).

#### Hexahydro -2- (hydroxymethyl) pyrrolo [1,2-b] isoxazole - 3- carboxylate Lactone (7):

A stirred solution of 0.9g (1.1 mmol) of 1-pyrroline 1-oxide 5,

0.9g (1.1 mmol) of 1-butenolide  $\overset{\curvearrowright}{6}$ , and 50 ml of dry benzene was refluxed for 48 hours. Evaporation of benzene under reduced pressure left a brown solid. Recrystallization using petroleum ether/dichloromethane (4:1) afforded white needles : 1.44g, 62% yield; m.p. 89 - 90°C; IR(KBr) 3.36 (m), 5.58 - 5.88(s), 7.25 (m), and 8.49  $\mu$ (s);  $^1\text{H}$  NMR(250 MHz,  $\text{CDCl}_3$ )  $\delta$  1.52 - 2.40 (cp, 4H), 3.00 - 3.40 (cp, 3H), 3.90 (t, 1H), 4.34 - 4.50 (cp, 2H), and  $\delta$  4.88 - 4.94 (m, 1H).

Hexahydro -2- methyl -2- (hydroxymethyl) pyrrolo [1,2-b] isoxazole -3- carboxylate Lactone ( $\overset{\curvearrowright}{11}$ ):

Hexahydro -2- methyl -2- (hydroxymethyl) pyrrolo [1,2-b] isoxazole -3- carboxylate Lactone( $\overset{\curvearrowright}{12}$ ):

A stirred solution of 0.50g (5.6 mmol) of 1-pyrroline-1-oxide  $\overset{\curvearrowright}{5}$ , 0.80 g (8.2 mmol) of 4-methyl -2(5H)-furanone  $\overset{\curvearrowright}{10}$ , and 50 ml of dry benzene was refluxed for 36 hours. Evaporation of benzene under reduced pressure left a brown oil which was subjected to column chromatography (silica gel, 3:7 (v/v) ethyl acetate/dichloromethane) to give two components in an approximate ratio of 75 : 25, corresponding to the exo- $\overset{\curvearrowright}{11}$  (mp 95-96°C) and endo -  $\overset{\curvearrowright}{12}$  isomers respectively: IR (KBr) $_{\text{exo}}$  3.38(m), 5.55 - 5.75(s), 6.85 (m), 7.25(m), and 7.70(m) $\mu$ ;  $^1\text{H}$  NMR(250 MHz,  $\text{CDCl}_3$ )  $\delta$  1.55 (s, 3H), 1.65 - 1.90 (cp, 2H), 2.08 (cp, 2H), 2.9 - 3.1 (cp, 2H), 3.40 - 3.50 (cp, 1H), 3.73 (t, 1H), 4.15 (d, 1H) and  $\delta$  4.50 (d, 1H).

IR (neat) $_{\text{endo}}$  3.40(s), 6.85(m), 7.27 (m), 7.88 (m), and 8.45 (s)  $\mu$ ;  $^1\text{H}$  NMR(250 MHz,  $\text{CDCl}_3$ )  $\delta$  1.58 (s, 3H), 1.72 - 2.0 (cp, 2H), 2.02 - 2.25 (cp, 2H) 2.92 - 3.08 (dd, 1H), 3.24 - 3.38 (cp, 2H), 4.0 - 4.12 (cp, 2H), and  $\delta$  4.35 (d, 1H).

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