

# AN ALTERNATIVE TOTAL SYNTHESIS OF (+)-PALLESCENSIN A BASED ON THE INTRAMOLECULAR [3+2] CYCLOADDITION REACTION

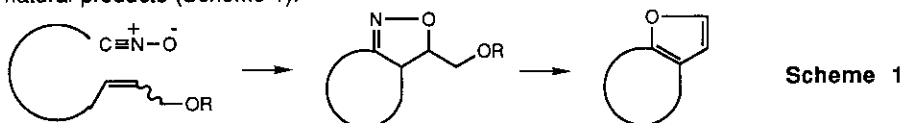
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**Abstract** - An alternative total synthesis of optically active pallescensin A is described which features a furan construction via the intramolecular [3+2] cycloaddition of nitrile oxide.

The [3+2] dipolar cycloaddition reactions of nitrile oxide have been widely exploited for the construction of several versatile functionalities in organic synthesis.<sup>1</sup> Recently, Tsuge and co-workers<sup>2</sup> reported a new method for the synthesis of substituted furans via the regioselective intermolecular cycloaddition of nitrile oxides to O-protected allyl alcohols. In connection with our current studies directed towards total synthesis of natural products using intramolecular pericyclic reactions,<sup>3</sup> we became interested in the development of intramolecular variant of this process which would be considerably useful for the synthesis of furan-fused polycyclic natural products (Scheme 1).

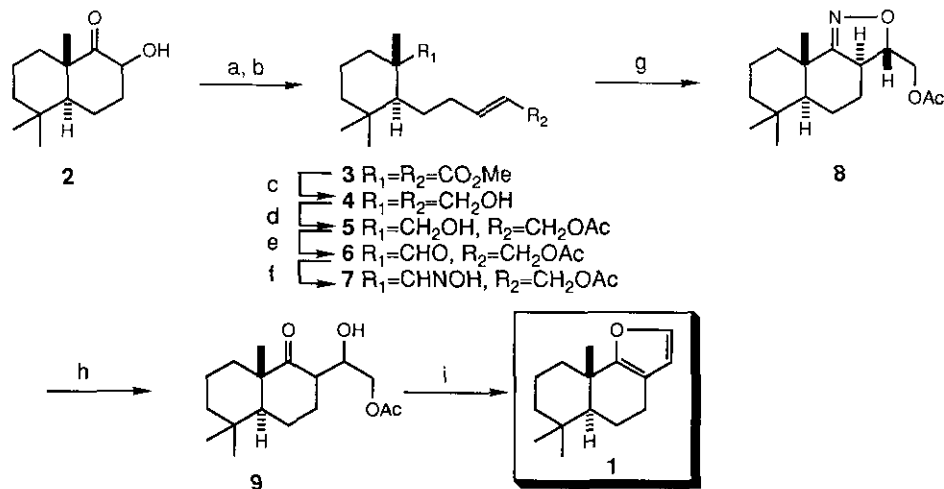


Scheme 1

This paper describes the successful use of the intramolecular strategy for a total synthesis of marine furanosesquiterpene (+)-pallescensin A (**1**).<sup>4</sup>

Oxidative cleavage of the hydroxy ketone (**2**),<sup>3,5</sup> readily derived from (+)-Wieland-Miescher ketone,<sup>6</sup> with lead tetraacetate in methyl alcohol followed by immediate Wittig reaction gave the diester (**3**) which was then reduced with diisobutylaluminum hydride to provide the diol (**4**) in 92 % overall yield from **2**. Selective acetylation of the allylic alcohol moiety in **4** using acetyl chloride was performed at 0 °C in the presence of diisopropylethylamine to provide **5** in 80 % yield. Transformation of **5** into the substrate for the cycloaddition was achieved by sequential Swern oxidation and a standard oxime formation to give the single oxime (**7**) in 85 % overall yield. Treatment of **7** with a solution of 7% aqueous sodium hypochlorite in methylene chloride at room temperature provided the isoxazoline (**8**)<sup>7</sup> as a single product in 91 % yield. Although the exact configuration of the newly formed chiral centers in **8** could not be determined by <sup>1</sup>H nmr analysis, the stereochemistry was indicated as depicted in Scheme 2 from the mechanistic point of view.<sup>3</sup> Finally, reductive hydrolysis of **8** with Raney nickel in the presence of trimethyl borate in aqueous methyl alcohol gave the hydroxy ketone (**9**) which was then hydrolyzed with lithium hydroxide followed by acid treatment to provide (+)-pallescensin A (**1**),<sup>8</sup> [  $[\alpha]_D^{25} +78.2^\circ$  (  $c=1.24$ , CHCl<sub>3</sub> ) ; lit.<sup>4c</sup> [  $[\alpha]_D^{25} +81.3^\circ$  (  $c=1.3$ , CHCl<sub>3</sub> ) ], in 62 % overall yield from **8**. The synthetic pallescensin A produced in this manner was shown to be identical with authentic material<sup>4a</sup> by comparison of their spectral data ( <sup>1</sup>H nmr and ir ).

Scope and limitation, as well as further applications of the present methodology will be reported in due course.



#### Reagents :

a,  $Pb(OAc)_4$ , MeOH ; b,  $Ph_3P=CHCO_2Me$  ; c, DIBAH ; d, AcCl,  $(i-Pr)_2NEt$  ; e,  $(COCl)_2$ , DMSO,  $Et_3N$  ; f,  $NH_2OH \cdot HCl$ , AcONa ; g, NaOCl ; h,  $H_2$ , Raney Ni,  $(MeO)_3B$  ; i, LiOH, aq. THF then HCl.

Scheme 2

#### ACKNOWLEDGMENT

We wish to thank Prof. T. Matsumoto ( University of Tokushima ) for providing spectra of authentic pallescensin A .

#### REFERENCES AND NOTES

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- J. Gutzwiller, P. Buchschacher, and A. Furst, *Synthesis*, 1977, 167. The optical rotation of Wieland-Miescher ketone used here is  $[\alpha]_D +92.0^\circ$  (  $c=1.0$ , benzene ).
- $[\alpha]_D -171.7^\circ$  (  $c=1.06$ ,  $CHCl_3$  ) ; mp  $79.5 - 80.5^\circ C$  ;  $^1H$  nmr ( 200MHz,  $CDCl_3$  )  $\delta$  : 0.90 ( 6H, s ), 1.18 ( 3H, s ), 1.11 - 1.82 ( 10H, m ), 2.05 - 2.19 ( 1H, m ), 2.08 ( 3H, s ), 3.02 - 3.14 ( 1H, m ), 4.10 - 4.30 ( 3H, m ).
- Colorless oil ; ir (  $CHCl_3$  ) : 2930, 2850, 1500, 1455, and  $1375\text{ cm}^{-1}$  ;  $^1H$  nmr ( 200MHz,  $CDCl_3$  )  $\delta$  : 0.91, 0.93, 1.19 ( 3H each, s ), 1.21 - 1.89 ( 8H, m ), 2.08 - 2.14 ( 1H, m ), 2.28 - 2.55 ( 2H, m ), 6.11 ( 1H, d,  $J=1.8$  Hz ), 7.18 ( 1H, d,  $J=1.8$  Hz ) ; ms (  $m/z$  ) : 218 (  $M^+$  ).

Received, 13th February, 1990