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

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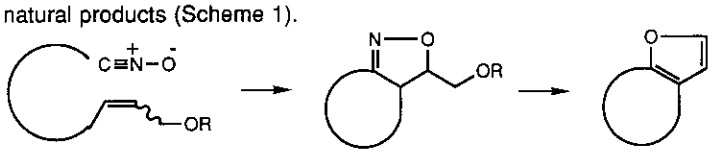
Abstract - An alternative total synthesis of optically active pallescensin A is described which features a furan construction via the intramolecular [3+2] cycloaddition of nitrile oxide.

The [3+2] dipolar cycloaddition reactions of nitrile oxide have been widely exploited for the construction of several versatile functionalities in organic synthesis.[1] Recently, Tsuge and co-workers[2] 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,[3] 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).

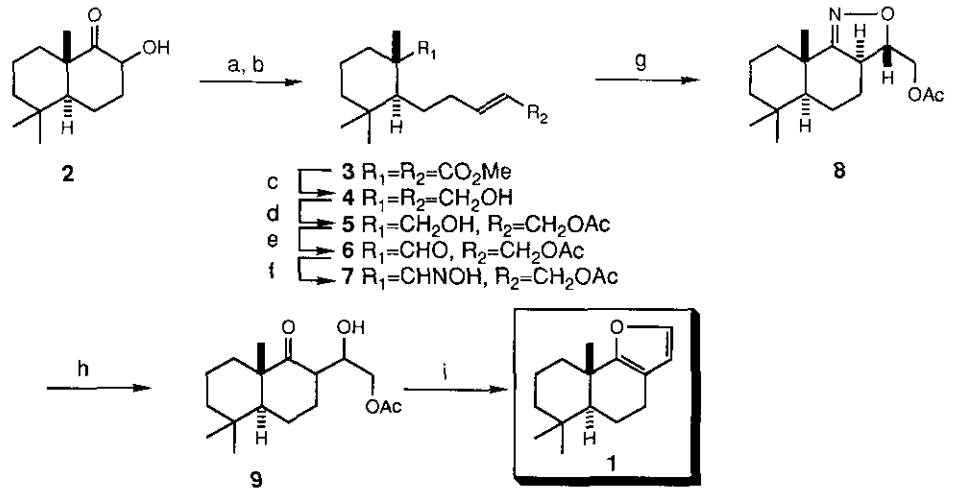


Scheme 1

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

Oxidative cleavage of the hydroxy ketone **(2)**,[3,5] readily derived from (+)-Wieland-Miescher ketone,[6] 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)**[7] as a single product in 91 % yield. Although the exact configuration of the newly formed chiral centers in **8** could not be determined by ^{1}H nmr analysis, the stereochemistry was indicated as depicted in Scheme 2 from the mechanistic point of view.[3] 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)**,[8] [$[\alpha]_D$ +78.2 °(c=1.24, $CHCl_3$) ; lit.[4c] $[\alpha]_D$ +81.3 °(c=1.3, $CHCl_3$)] , in 62 % overall yield from **8** . The synthetic pallescensin A produced in this manner was shown to be identical with authentic material[4a] by comparison of their spectral data (^{1}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, $(i\text{-}Pr)_2NEt$; e, $(COCl)_2$, DMSO, Et_3N ; f, NH_2OH•HCl, AcONa ; g, NaOCl ; h, H_2, Raney Ni, $(MeO)_3B$; i, LiOH, aq. THF then HCl.

Scheme 2

ACKNOWLEDGMENT

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REFERENCES AND NOTES

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4. Total syntheses of optically active pallescensin A : (a) T. Matsumoto and S. Usui, Chemistry Lett., 1978, 105 ; (b) H. Akita and T. Oishi, Chem. Pharm. Bull., 1981, **29**, 1580 ; (c) A. B. Smith, III and R. Mewshaw, J. Org. Chem., 1984, **49**, 3685.
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6. J. Gutzwiller, P. Buchschacher, and A. Furst, Synthesis, 1977, 167. The optical rotation of Wieland-Miescher ketone used here is $[\alpha]_D$ +92.0 °(c=1.0, benzene).
7. $[\alpha]_D$ -171.7 °(c=1.06, $CHCl_3$) ; mp 79.5 - 80.5 °C ; ^1H nmr (200MHz, $CDCl_3$) δ : 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).
8. Colorless oil ; ir ($CHCl_3$): 2930, 2850, 1500, 1455, and 1375 cm^{-1} ; ^1H nmr (200MHz, $CDCl_3$): δ : 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^+).

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