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. Recently, Tsuge and co-workers 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, 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).

This paper describes the successful use of the intramolecular strategy for a total synthesis of marine furanosesquiterpene (+)-pallescensin A (1). Oxidative cleavage of the hydroxy ketone (2), readily derived from (+)-Wieland-Miescher ketone, 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) as a single product in 91% yield. Although the exact configuration of the newly formed chiral centers in 8 could not be determined by 1H nmr analysis, the stereochemistry was indicated as depicted in Scheme 2 from the mechanistic point of view. 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), [α]D +78.2° (c=1.24, CHCl₃); lit. 4c [α]D +81.3° (c=1.3, CHCl₃), in 62% overall yield from 8. The synthetic pallescensin A produced in this manner was shown to be identical with authentic material by comparison of their spectral data (1H nmr and ir).

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

Reagents:
1. P(OAc)₃, MeOH
2. Ph₃P=CHCO₂Me
3. DIBAH
4. AcCl, (i-Pr)₂NEt
5. (COCl)₂, DMSO, Et₃N
6. NH₂OH-HCl, AcONa
7. NaOCl
8. Hz, Raney Ni, (MeO)₂B
9. UOH, aq. THF then HCl.

Scheme 2

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REFERENCES AND NOTES
1. For a recent review, see S. Kanemasa and O. Tsuge, Heterocycles, 1990, 30, 719.
7. [α]₀ -171.7° (c=1.06, CHCl₃); mp 79.5 - 80.5 °C; ¹H nmr (200MHz, CDCl₃) δ: 0.90 (6H, s), 1.18 (3H), 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 (CHCl₃): 2930, 2850, 1500, 1455, and 1375 cm⁻¹; ¹H nmr (200MHz, CDCl₃): 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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