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ACYLATION OF YNAMINES BY ENOL-LACTONES : A NEW METHOD OF STEREOSELECTIVE SPIROANNELATION.

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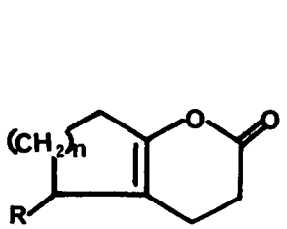
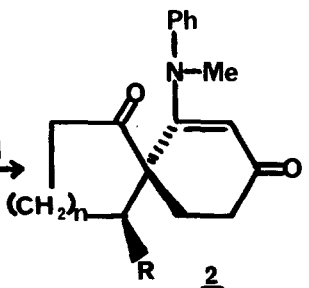
Summary : A new method of regio and stereoselective spiroannelation which leads to functionnalized spiro (4.5) decenes and (5.5) undecenes is described.

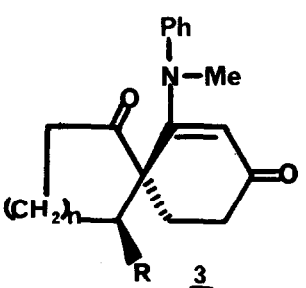
The stereoselective formation of quaternary spiro centers is a current problem[1] which occurs, in particular, in the synthesis of natural biologically active spirosesquiterpenes[2].

One of the major difficulties encountered in the synthesis of terpenes exhibiting this type of structure, for example acoradiene 5, concerns the control of the relative configuration of the quaternary spiro center and that of the chiral center present in the molecule.

In this paper, we report that acylation of ynamines by enol lactones[3], when they are bicyclic, constitutes a new method of spiro-annelation leading stereoselectively to spiro (4.5) decenes and spiro (5.5) undecenes of types 2 and 3.







1	2	3
a) n = 2 ; R = Me	85	15
b) n = 1 ; R = Me	80	20
c) n = 1 ; R = isoPr	100	0

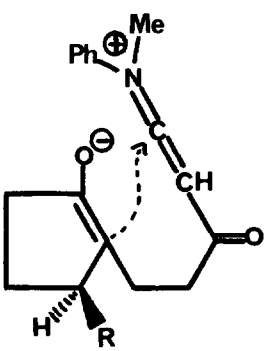
N-methyl N-phenylamino acetylene[4] (1 eq.) is introduced into an acetonitrile solution of enol lactone 1[5] (1 eq) to which has been added magnesium bromide (1 eq, 0.5 M solution in acetonitrile). After heating (4 hr, 70°C), washing with water and extraction with methylene chloride, the diastereoisomers 2 and 3 (yield : 60-70 %) are separated by chromatography on alumina, eluting with 4/1 hexane/ethyl acetate.

2a : [mp 111°C (ethyl acetate) ; IR (nujol) : 1690, 1640, 1550 cm^{-1} ; NMR ($CDCl_3$) : δ 1.0 (d,3H), 3.15 (s,3H), 5.5 (s,1H) ppm].
3a : [IR ($CHCl_3$) : 1690, 1640, 1550 cm^{-1} ; NMR ($CDCl_3$) : δ 1.3 (d,3H), 3 (s,3H), 4.95 (s,1H) ppm].
2b : [mp 132°C (ethyl acetate) ; IR ($CHCl_3$) : 1740, 1625, 1545 cm^{-1} ; NMR ($CDCl_3$) : δ 0.95 (d,3H), 3.05 (s,3H), 5.6 (s,1H) ppm].
3b : [mp 156°C (ethyl acetate) ; IR ($CHCl_3$) : 1740, 1625, 1545 cm^{-1} ; NMR ($CDCl_3$) : δ 1.1 (d,3H), 3 (s,3H), 5.15 (s,1H) ppm].
2c : [mp 168°C ; IR ($CHCl_3$) : 1730, 1630, 1550 cm^{-1} ; NMR ($CDCl_3$) : δ 0.9 (6H), 3.1 (s,3H), 5.7 (s,1H) ppm].

The structure of the diastereoisomers 2 and 3 were determined by X-ray diffraction analysis in the case of 2b and 3b[8].

These initial results show that the reaction of N-methyl N-phenylamino acetylene with the enol lactones 1 takes place with high stereoselectivity and that this selectivity depends on the steric hindrance of the group R on the enol lactone. In the three cases studied, the major isomer of type 2 is the one in which the group R is trans to the enamino ketone moiety. When the hindrance of R is great enough as in the case of isopropyl, we observe the exclusive formation of isomer 2c in which R is trans to the enamino-ketone and detect no trace of 3c.

This stereoselectivity can be rationalized by assuming, for example, the presence of an intermediate of type 4, formed after the initial attack of the ynamine on the lactonic carbonyl :



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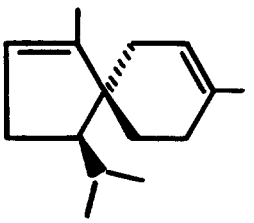
If such an intermediate is actually present, it should be neutralized by carbocyclization rather than by heterocyclization which would generate a less favorable 8-membered ring. In this carbocyclization, the approach of the ketene-immonium ion is faster on the less hindered side of the enolate, i.e., when the approach is trans to the substituent[9].

The new method of spiroannelation described here has been illustrated by the synthesis of a natural sesquiterpene of the acorane family, acoradiene 5, and this work is the subject of the following paper.



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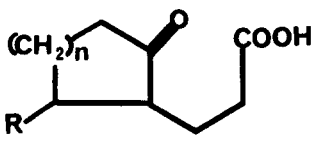
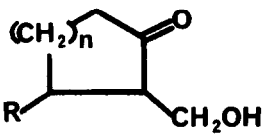
5) The enol lactones 1 : 1a : [IR (neat) : 1765, 1700 cm^{-1} ; NMR (CCl_4) : δ 1 (d,3H) ppm]; 1b : [IR (neat) : 1770, 1710 cm^{-1} ; NMR (CCl_4) : δ 1.05 (d,3H) ppm]; 1c : [IR (neat) : 1770, 1710 cm^{-1} ; NMR (CCl_4) : δ 0.85 (6H) ppm] are prepared (yield : 80 %) via cyclization by treatment[6] with p-toluenesulfonic acid (10 %, benzene, reflux, 1 hr) of the keto-acids 6, themselves obtained by malonic acid synthesis (yield : 70 %) starting from the keto-mesylates of keto-alkohol 7 produced regioselectively by the enolate trapping method of Stork[7] from the corresponding cyclic enones (yield : 50-80 %).



6 n = 1 or 2



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