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The Isoxazoline Route to α-Methylene Lactones.

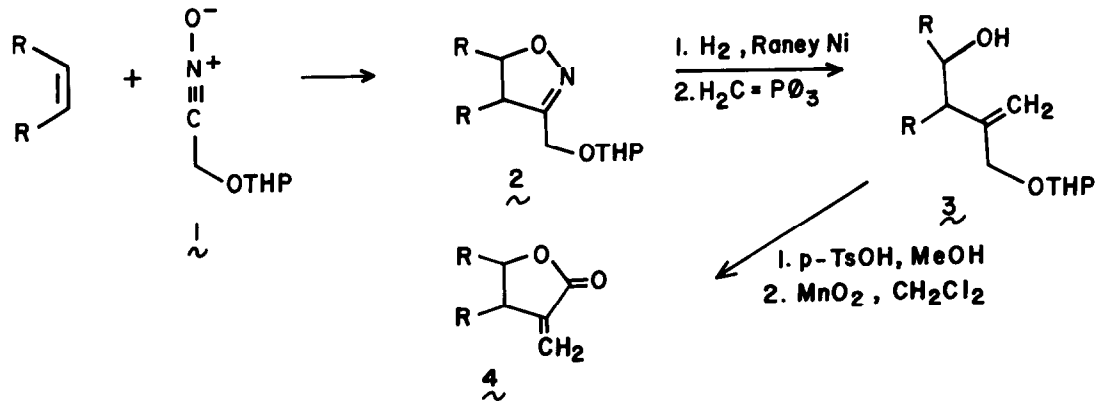
Alan P. Kozikowski* and Arun K. Ghosh
Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Summary: *A new route to α-methylene lactones, important structural subunits of many natural products, has been developed using the nitrile oxide derived from 2-nitroethanol.*

In order to further expand the importance of isoxazolines as versatile vehicles for natural product synthesis,[1] we have undertaken recently a study which reveals their ability to function as precursors to α-methylene lactones. While much effort has already been expended on the development of routes to these important structural subunits,[2] we believe that the chemistry outlined in this letter does constitute a fairly unique and in some instances a useful approach to these substances. The overall process is quite straightforward and begins with the dipolar cycloaddition reaction of the nitrile oxide derived from the tetrahydropyranyl ether derivative of 2-nitroethanol[3] with the alkene of choice. Phenyl isocyanate/triethylamine is used to effect conversion of the nitro compound to its nitrile oxide 1. The absence of β-elimination with this nitroethanol derivative is noteworthy and presumably a consequence of the high stability of the nitronate anion coupled with the poor leaving group ability of the tetrahydropyranyloxy group.

The isoxazoline product 2 derived from the dipolar cycloaddition reaction is cleaved by hydrogenolysis utilizing Raney nickel in a mixture of acetic acid, methanol and water (1:8:2).[4] The resulting β-hydroxy ketone is exposed to excess methylenetriphenylphosphorane to yield a homoallylic alcohol 3. Removal of the tetrahydropyranyl group (p-TsOH) and manganese dioxide[5] treatment of the diol then complete the α-methylene lactone synthesis.

SCHEME I An α-Methylene Lactone Synthesis



These general reaction conditions sufficed for the preparation of the methylene lactones listed in entries 1-4 of Table I. In the case of entry 5, PPTS was used for cleavage of the tetrahydropyranyl group, for p-toluenesulfonic led instead to dehydration of the intermediate tertiary alcohol. Application of the same overall strategy to cyclopentene was troubled by epimerization at the stage of isoxazoline cleavage. In this instance, H_2/Raney Ni/BCl_3/MeCH/H_2O was used to effect conversion to the β-hydroxy ketone without competing epimerization. Execution of the remaining steps as above then yielded the desired cis-fused lactone (entry 6).

We also note here that it is possible to further abbreviate the overall strategy by employing Oshima's Zn-$TiCl_4$-CH_2Br_2 system[6] to effect methylenation of the intermediate β-hydroxy ketone, for this one-carbon homologation step proceeds with concomitant cleavage of the tetrahydropyranyl group (e.g. 5 → 7).

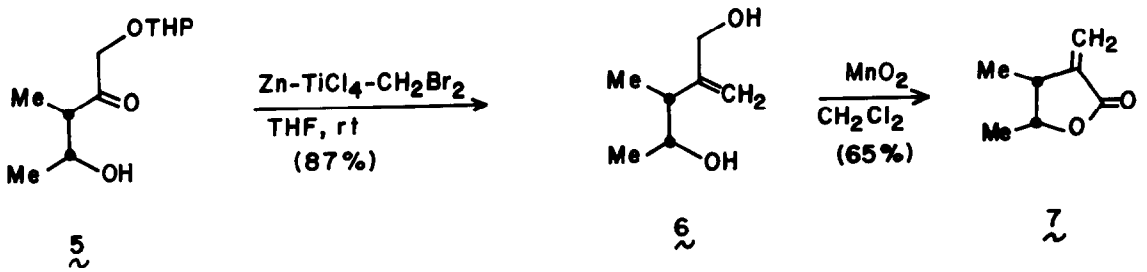
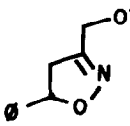
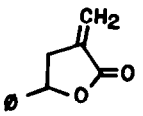
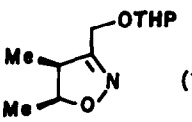
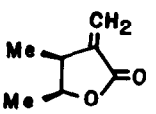
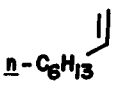
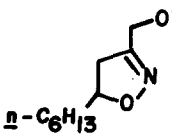
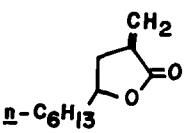
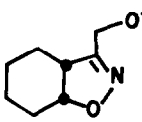
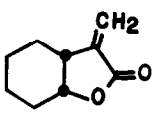
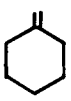
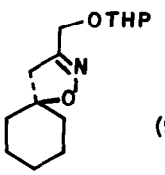
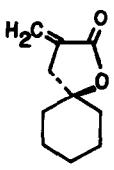
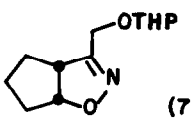
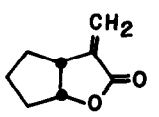
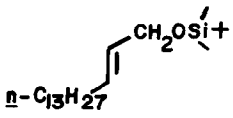
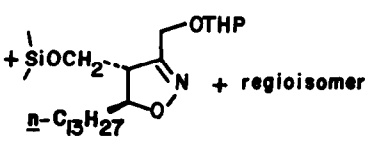
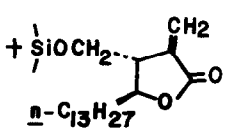


Table I. Synthesis of α-Methylene Lactones from Isoxazolines

Entry	Alkene	Isoxazoline (yield %)[a]	α-Methylene Lactone (yield % overall from isoxazoline)[a]
1.		 (86)	 (49)
2.		 (74)	 (56)
3.		 (77)	 (47)
4.		 (64)	 (27)
5.		 (98)	 (50)
6.		 (77)	 (40)
7.		 (88%; ~88:12)	 (73)

[a]The yields were calculated after purification of the products by silica gel chromatography.

Reaction of 1 with the allylic alcohol derivative shown in entry 7 proved moderately regioselective with the oxygen end of the dipole adding largely away from the silyl ether group (ratio ∿ 88:12). The use of Raney Ni/BCl_3/i-PrOH/H_2O in the hydrogenation step permitted N-O bond cleavage to proceed without competing O-desilylation. Methylenation by Oshima's method and manganese dioxide oxidation gave rise to the functionalized α-methylene lactone, a potential precusor to protolichesterinic acid.[7,8]

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References and Notes

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7. E. E. van Tamelen and S. R. Bach, J. Am. Chem. Soc., 80, 3079 (1958) and references cited therein.
8. Satisfactory IR, ^1H NMR, and mass spectral data were obtained for all new compounds. Exemplary IR and 300 MHz ^1H NMR data for the isoxazoline and α-methylene lactone reported in entry 5 follow: isoxazoline, IR (film) 2905, 1725, 1600, 1230 cm^{-1}; NMR ($CDCl_3$) δ 4.63 (m, 1 H), 4.33 (ABq, 2 H, J = 12.63 Hz ν_{AB} = 37.16), 3.85 (m, 1 H), 3.52 (m, 1 H), 2.75 (s, 2 H), 1.30-1.90 (m, 16 H); α-methylene lactone, IR (film) 1760, 1660 cm^{-1}; NMR ($CDCl_3$) δ 6.23 (t, 1 H, J = 2.72 Hz), 5.61 (t, 1 H, J = 2.72 Hz), 2.71 (t, 2 H, J = 2.72 Hz) 1.20-1.90 (m, 10 H).

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