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REVERSIBLE THIOL ADDITION AS A PROTECTING REACTION FOR CONJUGATED α-METHYLENE GROUPS OF LACTONES

S. Morris Kupchan, Thomas J. Giacobbe, and Ira S. Krull

Department of Chemistry, University of Virginia,

Charlottesville, Virginia 22901, and

Department of Pharmaceutical Chemistry, University

of Wisconsin, Madison, Wisconsin 53706

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A new blocking sequence is presented for the protection of the highly reactive conjugated α-methylene groups of lactones.

The need for a method for protecting α-methylene groups conjugated with both γ- and δ-lactones arose during a study of the requirements for biological activity among derivatives of vernolepin (1).[1] The synthesis of 1,2-dihydrovernolepin was undertaken for an evaluation of the potential significance of the ethylidene group. Direct selective hydrogenation of the ethylidene double bond was deemed impractical, because earlier studies had shown that hydrogenation of vernolepin led either to 1,2,11,13-tetrahydrovernolepin[2] or to 1,2,4,11,13,15-hexahydrovernolepin.[3]

A solution of vernolepin (1) and 1-propanethiol in tetrahydrofuran was treated with pH 9.2 borate buffer and the mixture was stirred at room temperature for 18 hours. Extraction with chloroform followed by chromatography on SiliCAR-CC7 gave the oily bis-1-propanethiol adduct 2: $C_{21}H_{32}O_5S_2$;[4] nmr ($CDCl_3$) τ 4.38 (3H, m, -C<u>H</u>=C<u>H</u>$_2$), 9.00 (6H, t, <u>J</u> = 7 Hz, 2 -CH_2C<u>H</u>$_3$); ir ($CHCl_3$) 1785, 1735 cm^{-1}; mass spectrum m/e 428 (M^+). The reversibility of the adduct formation was demonstrated by methylation of 2 with methyl iodide and trituration of the sulfonium salt with a saturated solution of sodium bicarbonate, whereupon vernolepin was regenerated. Hydrogenation of adduct 2 with 10% palladium on carbon yielded oily 1,2-dihydrovernolepin bis-1-propanethiol adduct (3): $C_{21}H_{34}O_5S_2$; nmr ($CDCl_3$) τ 9.00 (9H, t, <u>J</u> = 7 Hz, 3 -CH_2C<u>H</u>$_3$), no vinyl proton signals; ir ($CHCl_3$) 1785, 1735 cm^{-1}; mass spectrum m/e 430 (M^+). Treatment of 3

with methyl iodide and trituration of the crude product with saturated sodium bicarbonate solution gave 1,2-dihydrovernolepin (4): $C_{15}H_{18}O_5$; mp 146-147°; $[\alpha]_D^{28°}$ + 71° (c 1.02, acetone); uv λ_{end}^{MeOH} 208 mμ (ε 17,100); ir (KBr) 1775, 1720 cm^{-1}; nmr[5] ($CDCl_3$) τ 3.29 and 4.05 (2H, br s, C-15H_2), 3.80 and 3.93 (2H, d, J = 3 Hz, C-13H_2), 5.77 (1H, d, J = 12 Hz, C-14H), 6.09 (1H, dd, J = 12, 1.5 Hz, C-14H), 6.20 (1H, t, J = 11 Hz, C-6H), 9.07 (3H, t, J = 7 Hz, -CH_2CH_3); mass spectrum m/e 278 (M^+).

The usefulness of the new protecting reaction has been demonstrated in the interrelation of elephantopin with deoxyelephantopin, described in the accompanying report.[6]

A recent communication has reported the use of dimethylamine addition as a protecting reaction for conjugated α-methylene groups of lactones.[7] The removal of this protecting group, however, involved conversion of the amine adduct to the corresponding methiodide and pyrolysis, under conditions which limit the scope of the blocking sequence. Furthermore, studies of relative nucleophilic reactivities of amino groups and mercaptide ions in addition reactions with α,β-unsaturated compounds have demonstrated the markedly greater reactivity of sulfur anions.[8,9]

Two recent studies have lent support to the view that Michael-type addition of sulfhydryl-bearing biological macromolecules to tumor-inhibitory α-methylene lactones may play a significant role in the mechanisms by which the lactones exert their biological activities.[9,10] In view of the observed ease of the "retro-Michael" reaction of the sulfonium salts of the thiol adducts, it is tempting to speculate that the selectivity reflected in the in vivo tumor-inhibitory activity of α-methylene lactones[1] may be related to the relative ease with which thioethers are methylated in normal and in neoplastic tissues. Investigations are in progress to determine the potential significance of reversible thiol addition and other reactions in relation to the tumor-inhibitory activity of α-methylene lactones.

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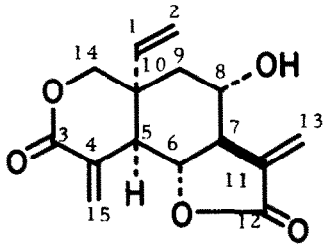

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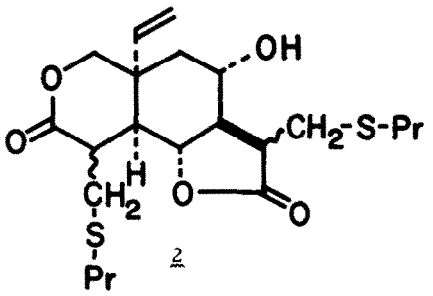

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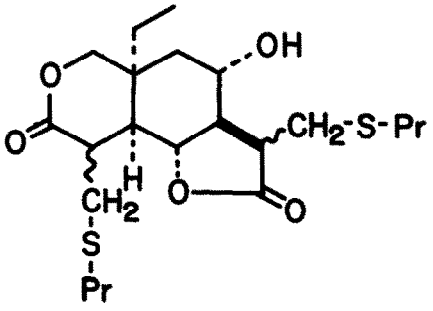

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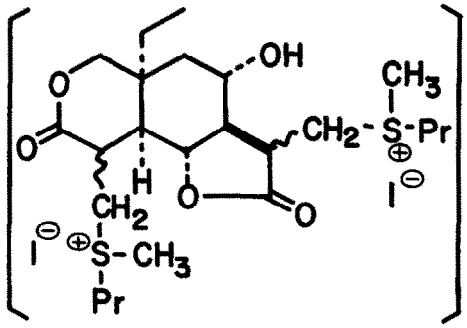

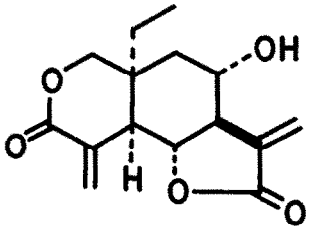

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