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THE ALKYLATION AND ALDOLIZATION OF LACTONE ENOLATES DERIVED BY THE CONJUGATE ADDITION OF AN ARYL DITHIANE ANION TO 2-BUTENOLIDE: A SYNTHESIS OF (±)PODORHIZOL AND (±)EPIPODORHIZOL.

Frederick E. Ziegler[1] and John A. Schwartz

Sterling Chemistry Laboratory, Yale University, New Haven, Connecticut 06520

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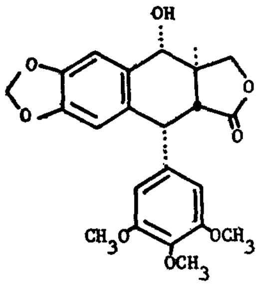
Bis-benzylbutyrolactones such as podophyllotoxin 1,[2] steganacin 2a, and steganangin 2b[3] have been shown to have cytotoxic activity toward human carcinoma. Since *seco*-lactone 5a has been converted to a mixture of desoxypodophyllotoxin and isodesoxypodophyllotoxin,[4] it was our intention to develop a reaction sequence which would efficiently construct the *seco*-lactone skeleton and contain functionality necessary for possible elaboration to the cyclic lactones 1, 2a, and 2b.

Lithiation (BuLi, THF-hexane, -78°, 1 hr, N_2) of piperonal dithiane[5] followed by treatment with 2-butenolide (1 hr, -78°) provided the Michael adduct 3a (mp 154-5°; ir($CHCl_3$)1780 cm^{-1}; 88%).[6] Dithiane cleavage (HgO-BF_3, aq. THF)[7] gave rise to the ketolactone 3b (mp 118-119°; ir($CHCl_3$)1675 and 1780 cm^{-1}).

Treatment of lactone 3a with lithium diisopropylamide (LDA) (THF-hexane, -78°, 1 hr.) followed by the addition of 3,4,5-trimethoxybenzyl chloride (THF-HMPA, 3 hrs. -78°, then 18 hrs. at R.T.) gave rise to the mono alkylated lactone 4a (mp 146-146.5°; nmr δ($CDCl_3$) 3.83 (9H,s, OCH_3), 4.03 (1H,d,J = 10 Hz), 4.64 (1H,dd,J = 6,10 Hz), 6.03 (2H,-OCH_2O-), and 6.25 (2H,s). More efficiently, the lactone enolate generated by Michael addition could be directly alkylated *in situ* (65% yield) to provide the same product of alkylation.

Removal of the dithiane moiety was readily effected (HgO-BF_3, aq. THF, R.T. 2 hrs) to afford ketolactone 4b (mp 142-143.5°; (lit[8] 140-143°) 95%). While N-iodosuccinimide in aqueous acetone provided the same lactone, N-bromosuccinimide[9] gave the bromoketolactone 4c.

Treatment of the dithiane lactone enolate with 3,4,5-trimethoxybenzaldehyde (-78°, N_2, THF) yielded a 52/48 mixture (5b/6b) by hplc. Upon fractional crystallization from ethyl acetate alcohol 5b (mp 205-206°; ir($CHCl_3$) 3490, 1755 cm^{-1}; nmr δ($CDCl_3$)4.97(1H,d,J = 9 Hz, -C<u>H</u>-OH); 50% yield) and 6b (mp 180-181°; ir($CHCl_3$) 3500, 1760 cm^{-1}; nmr δ ($CDCl_3$) 4.77 (1H,d,J = 5.5 Hz, -C<u>H</u>OH) were isolated. When aldolization was performed in 1:1 glyme-ether, the *threo* isomer 6b predominated in a 3/1 ratio.[10]



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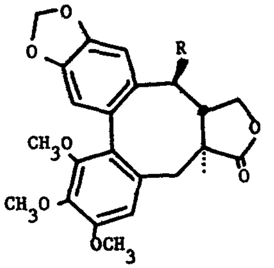
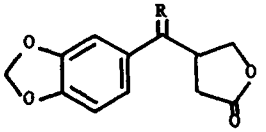


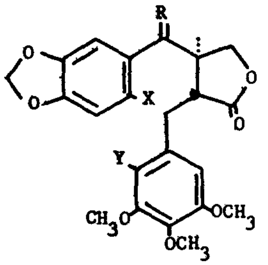
2a $R = OAc$

b $R = Z\text{-}O_2CCCH_3{=}CHCH_3$



3a, $R = -S(CH_2)_3S-$

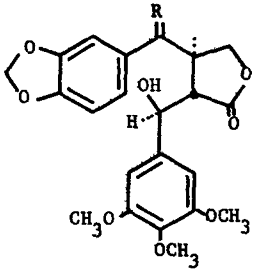
b, $R = O$



4a, $R = -S(CH_2)_3S-, X = Y = H$

b, $R = O$, $X = Y = H$

c, $R = O$, $X = H$, $Y = Br$



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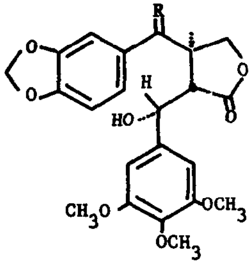

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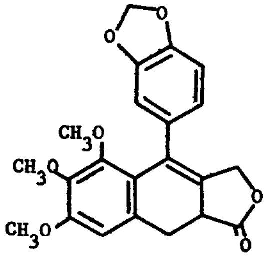
a, $R = H_2$

b, $R = -S(CH_2)_3S-$

c, $R = O$

Desulfurization of dithiane 5b (Ni(R), EtOH, reflux, 3 hrs., N_2) provided (±)podorhizol in 72% yield which was identical (solution ir, 270 MHz, nmr, tlc, hplc) with a sample from natural sources. In a similar fashion (±)epipodorhizol was formed in 74% yield.

Attempted cyclization of lactone 4a as described[11] by Ronlan and Parker (Mn(acac)$_3$, F_3CCO_2H - CH_2Cl_2, -20° or anodic oxidation, F_3CCO_2H - CH_2Cl_2, -20°) provided not the eight-membered ring but the six-membered ring lactone 7(mp 180-181°; ir($CHCl_3$) 1770 cm^{-1}; nmr δ($CDCl_3$) 3.35, 3.79, 3.82 (9H,s,OCH_3), 4.71 (1H,dd,J = 3.5,16 Hz) and 5.12 (1H,dd,J = 3.5,16 Hz); 50% yield.



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These reaction conditions, as well as a variety of acid reagents, left the ketone 4b unchanged.

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