be hemolytic and the saponins, whose genuine sapogenins are 20-S-protopanaxadiol, were protective from the hemolysis by the former saponins and by other hemolytic reagents. Panaxadiol and panaxatriol, which are the artifacts derived from the genuine sapogenins during the acid hydrolysis of saponines, did not show any activity of hemolysis and protection either. Studies on the correlationship between hemolytic and protective activities and chemical structure of saponin in general are now in progress.

Takagi, *et al.*[2] reported that Rg group stimulated the central nervous system and Rb group showed sedative effect. In our present study, we found that some fractions of ginseng saponins were hemolytic and the others were contrarily anti-hemolytic. Both components were present in one Chinese crude drug and, with deep interest, both activities are apparently masked in a crude preparation owing to their ballanced counter-activity. The facts may explain the principle of the double-faced effects in the traditional Chinese medicine where the same drugs were properly applied, dependent upon the constitution and condition of patients of different diseases.

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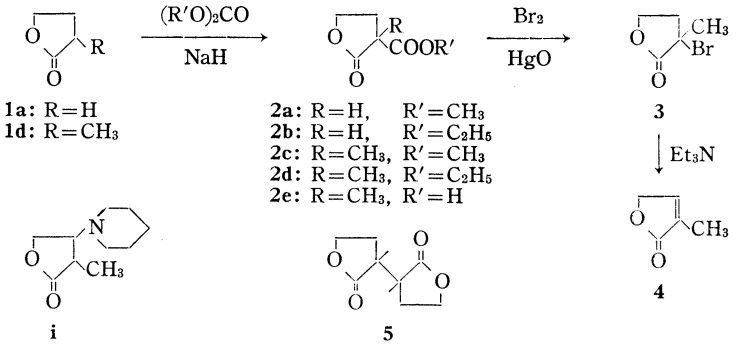
A New Synthetic Pathway to $\Delta^{\alpha,\beta}$-Butenolide from γ-Butyrolactone[1]

Various substances containing saturared and unsaturated γ-butyrolactone moiety in each molecule have been well found to occur widely in the plant kingdom. In the course of our studies on chemistry of physiologically active sesquiterpenolides, we have recently deviced an interesting method being useful for transformation of α, β-unsaturated γ-butyrolacetone from the corresponding saturated homologue.

The present communication describes a preliminary account for the synthetic pathway to $\Delta^{\alpha,\beta}$-butenolide from α-methyl-γ-butyrolactone involving a new sequence of carboxylation-bromination-dehydrobromination reactions. The application of the ordinary synthetic operation for bromination of the ester or lactone grouping brings about little promise, even in the case of apparent simple lactones. So the possible introduction of the carboxyl group at α-position of the lactonic carbonyl would be first envisaged for an attempted modification. As far as we are aware in the references, there are no precedences for carboxylation of the lactones. Now it is of special interest to note that alkoxycarbonylation of the simplest γ-

1) Presented to the 92nd annual meeting of the Pharmaceutical Society of Japan, Osaka, April 1972; paper abstract II, p. 191.



A New Synthetic Route to α-Methyl-$\Delta^{\alpha,\beta}$-γ-butenolide from α-Methyl-γ-butyrolactone.

butyrolactone (**1a**) affording α-methoxycarbonyl-(**2a**) ($C_6H_8O_4$, M^+ 144, bp_{15} 145°) and α-ethoxycarbonyl derivative (**2b**) ($C_7H_{10}O_4$, M^+ 158, bp_{20} 155°)[2] was successively achieved by refluxing the salt of **1a** with methoxycarbonate and ethoxycarbonate with or without anhydrous solvent such as benzene or ether in a fairly good yield (~60%). **1a**: ν_{max}^{Film} (cm^{-1}) 1779, 1741, 1151, 1021. δ($CDCl_3$): 3.73 s (3H), 2.55 d,d,d 8,8,8 (2H), 3.57 q, 8 (1H), 4.38 d, 8 (1H), 4.35 d, 8 (1H). **1b**: ν_{max}^{Film} (cm^{-1}) 1780, 1740, 1152, 1024. δ($CDCl_3$): 1.33 t, 7 (3H), 2.58 d,d,d 8,8,8 (2H), 3.59 q, 8 (1H), 4.28 q, 7 (2H), 4.38 d, 8 (1H), 4.42 d, 8 (1H). The syntheses of α-methoxycarbonyl-(**2c**) ($C_7H_{10}O_4$, M^+ 158, bp_{17} 135°) and α-ethoxycarbonyl-α-methyl-γ-butyrolactone (**2d**) ($C_8H_{12}O_4$, M^+ 172, bp 260°)[2] were carried out by the same manner as mentioned above except only in the presence of catalytic amount of HMPA in moderate yield (~40%). **2c**: ν_{max}^{Film} (cm^{-1}): 1780, 1745, 1270, 1218, 1178, 1144, 1090, 1024. δ($CDCl_3$): 3.71 s (3H), 1.48 s (3H), 1.75—2.95 m (2H), 4.30 d, 8 (1H), 4.40 d, 8 (1H). **2d**: ν_{max}^{Film} (cm^{-1}): 1780, 1744, 1270, 1217, 1181, 1145, 1091, 1025. δ($CDCl_3$): 1.37 t, 8 (3H), 1.49 s (3H), 1.90—2.30 m (2H), 4.20 q, 8 (2H), 4.33 d, 8 (1H), 4.40 d, 8 (1H). The lactonic esters (**2c** and **2d**) were further hydrolysed very smoothly with dilute hydrochloric acid to give rise to α-hydroxycarbonyl-α-methylbutyrolactone (**2e**)[2]: $C_6H_8O_4$, mp 98°, ν_{max}^{KBr} (cm^{-1}): 3000—2500, 1770, 1708. δ(DMSO-d_6): 1.48 s (3H), 1.9—2.9 m (2H), 4.34 m (2H).

In the next stage of our route towards the present target, α-methylbutenolide (**4**)[3] a consecutive reaction of decarboxylative bromination of the lactonic acid (**2e**) progressed quantitatively by action of equimolar bromine in hot carbontetrachroride in the presence of freshly prepared mercuric oxide under irradiation of a low pressure ultraviolet lamp affording α-bromo-α-methylbutyrolactone (**3**). $C_4H_7O_2Br$, M^+ 178, 180, bp_5 101°; ν_{max}^{Film} (cm^{-1}): 1782. δ($CDCl_3$) 1.92 s (3H), 2.1—2.8 m (2H), 4.37 m (2H). On the other hand, an attempted oxidation with lead tetraacetate in benzene and pyridine did producce neither the desired $\Delta^{\alpha,\beta}$-butenolide nor the lactonic acetate, but gave in poor yield a dimeric lactone, 2-methyl-2-[2'-methyl-2'-butyrolactonylbutyrolactone (**5**). $C_{10}H_{14}O_4$, M^+ 198, mp 119°; ν_{max}^{Film} (cm^{-1}): 1760, 1206, 1195, 1088, 1023. δ($CDCl_3$): 1.39 s (6H), 1.95 d,d,d 2,12,12 (2H), 2.98 d, 2 (2H), 4.1—4.55 m (4H). When the bromolactone (**3**) was subsequently submitted to a milder dehydrobromination (80—90°, 3 hr) with organic bases such as triethylamine or piperidine,[4] it exclusively afforded the requisit α-methylbutenolide (**4**)[3,5] without formation of another $\Delta^{\alpha,\beta}$-

2) R. Marburg, *Ann.*, **294**, 106 (1897).

3) *a*) C.J. Cavallito and T.H. Haskell, *J. Am. Chem. Soc.*, **68**, 2332 (1946); *b*) W.H. Huff and H.M. Sell, *ibid.*, **74**, 3183 (1952); *c*) M. Franck-Neumann and C. Berger, *Bull. Soc. Chim. Fr.*, **10**, 4067 (1968); *d*) A. Loeffler, R.J. Pratt, H.P. Ruesch, and A.S. Dreiding, *Helv. Chim. Acta.*, **53**(2), 383 (1970); *e*) A. Loeffler, F. Norries, W. Taub, K.L. Svanholt, and A.S. Dreiding, *ibid.*, **53**(2), 403 (1970).

4) A minor amount of β-[N-piperidyl]-α-methyl-γ-butyrolactone (**i**), being secondarily derived from **4**, can be detected in an acid part of the reaction product with piperidine.

5) Unpublished data show that the exo-product (**4**,$\Delta^{2,5}$) is predominant rather than the endo-product (**4**) in a modified dehydrobromination in certain system.

butenolide, α-methylene-γ-butyrolactone (**4**, $\Delta^{2,5}$).[6] **4**: $C_5H_6O_2$, M^+ 98, bp_6 75°; ν_{max}^{Film} (cm^{-1}): 1760, 1660. $\delta(CDCl_3)$: 1.97 m (3H), 4.80 m (2H), 7.18 m (1H).

Finally, we should mention parenthetically that the present new synthetic approach may be evident to point an useful template for a new direct route to the naturally occuring $\Delta^{\alpha,\beta}$-α-methylbutenolides from the α-methyl-γ-butyrolactones in natural abundance, apart from some approach[3] started from chemicals other than γ-butyrolactones. It might be plausible to assume that this synthetic approach *in vitro* would impregnate a similar sequence of reactions being carried out by appropriate biochemical equivalents *in vivo*.

Our studies on application of this useful device to the α-methyl-γ-butyrolactone containing some more complicated system is now in progress.

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