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A NEW APPROACH TO α-METHYLENE-γ-BUTYROLACTONES. SYNTHESIS OF (-)-FRULLANOLIDE.

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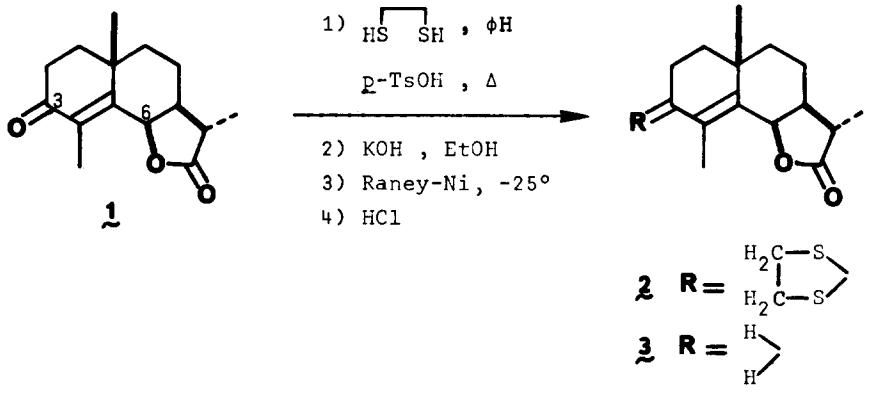
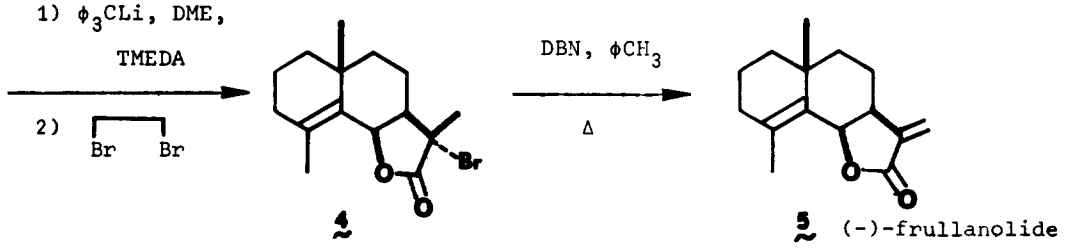
Efficient construction of the α-methylene-γ-butyrolactone moiety is a synthetic challenge which has received much attention during the past few years[1]. Many ingenious synthetic schemes have resulted but none permits access to this widely occurring[2,3] and often biologically active[3] grouping *via* the corresponding α-methyllactone. This transformation is of definite interest since appropriate α-methyllactone precursors are often readily available from synthetic procedures[4] and/or natural sources[2,3].

We now wish to report the synthesis of (-)-frullanolide, **5**, an allergenically active α-methylenebutyrolactone sesquiterpene first isolated in this laboratory[5], and thereby to demonstrate the utility of a potentially general technique for achieving the α-methyl→α-methylene conversion for *cis*-fused γ-butyrolactones.

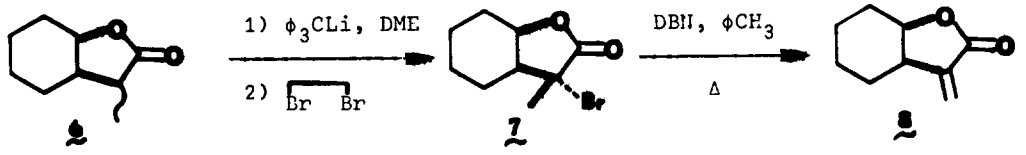
1,2-Dihydro-6-episantonin[6], **1**, was secured from α-santonin[7] in 90% overall yield. Removal of the C-3 ketone oxygen in **1** in the presence of the easily cleaved C-6 axial lactone oxygen was effected using modifications of the general[8] thioketalization–reduction procedure. The known thioketal **2** was obtained in a much improved yield[9] (>90%) by heating **1** in benzene with excess ethanedithiol in the presence of a catalytic amount of *p*-toluenesulfonic acid. Initial attempts to reduce **2** with Raney-nickel in abs. ethanol at room temperature led solely to acidic material by hydrogenolysis of the C-6/O bond[10]. However, the hydroxy-acid salt, obtained by treatment of **2** with KOH–95% EtOH, proved to be less prone to hydrogenolysis. Thus, the salt was stirred with W-2 Raney-nickel (10ml/g of **2** in 95% EtOH containing excess KOH, -25°, 2 hr) and then acidified and chromatographed to give **3** in better than 40% overall yield[11,12]: mp 119-121° ; $[\alpha]_D$ = -58° ($CHCl_3$) ; IR $\lambda_{max}^{CHCl_3}$ 1750 and 1645 cm^{-1} ; NMR $\delta_{TMS}^{CDCl_3}$ 5.43 (d, J=5Hz, 1H), 2.42 (q, J=8Hz, 1H), 1.77 (s, 3H), 1.33 (d, J=8Hz, 3H), and 1.07 ppm (s, 3H) ; $M^{+\cdot}$ = 234 (calc. 234) ; Anal. Calc. for $C_{15}H_{22}O_2$: C 76.88, H 9.46 ; Found: C 76.57, H 9.40.

Treatment[6] of 3 with excess triphenylmethyllithium in dimethoxyethane(DME) at 5° in the presence of tetramethylethylenediamine (TMEDA) gave the corresponding enolate, which, upon quenching with 1,2-dibromoethane[13] at 5°, afforded a single α-bromolactone, 4, in ca. 50% yield : IR $\lambda_{max}^{CHCl_3}$ 1775 cm^{-1} ; NMR $\delta_{TMS}^{CDCl_3}$ 5.68 (d, J=4Hz, 1H), 1.92 (s, 3H), 1.80 (s, 3H), and 1.01 ppm (s, 3H) ; $M^{+\cdot}$ = 312, 314 (calc. 312, 314). The stereochemical assignment was made on the basis of steric considerations, NMR evidence (deshielding of C-6 H), and on the subsequent direction of elimination of HBr. Dehydrobromination (excess diazabicyclononene (DBN), toluene, reflux, 1 hr) afforded (-)-frullanolide, 5, (mp 75-76°, $[\alpha]_D$ = -112°) in 80% yield, chromatographically and spectroscopically identical with authentic material obtained from Frullania tamarisci (L.) Dum[5].

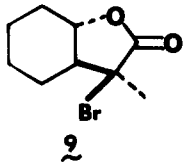




In the preliminary experiments, similar treatment of the cis-lactone[1a] 6 had cleanly afforded via a single bromide 7 the known[1a] α-methylene-γ-butyrolactone 8 in 60% overall yield (cf. reference 1).



No endocyclic olefin (formally requiring a cis elimination) was detected from treatment of either of the α-bromo-cis-lactones 4 or 7. In contrast, the α-bromo-trans-lactones 9 and 10 (formed in ∿60% and 75% yields, respectively, under the bromination conditions 6 → 7) gave exclusively endocyclic olefins under a variety of elimination conditions[14]. A complementary procedure for α-methyl–α-methylene conversion for such trans-fused γ-butyrolactones is presently being pursued.



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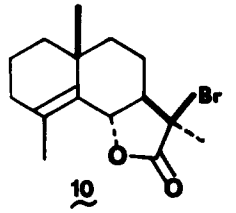

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References

1. a) J.A. Marshall and N. Cohen, J. Org. Chem., 30, 3475 (1965). b) H. Minato and I. Horibe, J. Chem. Soc. (C), 1575 (1967). c) J. Martin, P.C. Watts and F. Johnson, Chem. Comm., 27 (1970). d) E.S. Behare and R.B. Miller, ibid., 402 (1970). e) E. Öhler, K. Reininger and U. Schmidt, Angew. Chem., 82, 480 (1970). f) J.W. Patterson and J.E. McMurry, Chem. Comm., 488 (1971). g) L.K. Dalton and B.C. Elmes, Australian J. Chem., 25, 625 (1972).

2. Cf. G. Ourisson, S. Munavalli and C. Ehret, "Données relatives aux Sesquiterpénoïdes", Pergamon Press, Paris, 1966.

3. S.M. Kupchan, M.A. Eakin and A.M. Thomas, J. Med. Chem., 14, 1147 (1971) and references cited. J.C. Mitchell and G. Dupuis, Br. J. Derm., 84, 139 (1971) and references cited.

4. For examples of various high yield synthetic procedures leading to α-methylbutyrolactones see : a) E.W. Colvin, R.A. Raphael and J.S. Roberts, Chem. Comm., 858 (1971). b) E.I. Heiba and R.M. Dessau, J. Amer. Chem. Soc., 93, 995 (1971). c) D.H.R. Barton and A.J.L. Beckwith, Proc. Chem. Soc., 335 (1963). d) F.D. Gunstone and R.M. Heggie, J. Chem. Soc., 1354 (1952). e) Y. Abe and M. Sumi, J. Pharm. Soc. Japan, 72, 652 (1952).

5. H. Knoche, G. Ourisson, G.W. Perold, J. Foussereau and J. Maleville, Science, 166, 239 (1969).

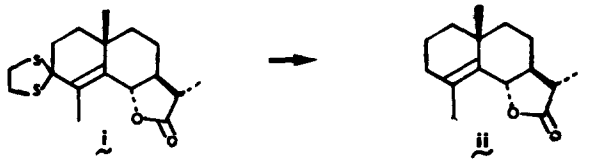
6. A.E. Greene, J-C. Muller and G. Ourisson, Tetrahedron Letters, 4147 (1971).

7. Purchased from Coopérative Pharmaceutique Française, S.A. Meulun. $[\alpha]_D$ = -176° ($CHCl_3$).

8. Cf. C. Djerassi, "Steroid Reactions", Holden-Day, Inc., San Francisco, 1963, pp. 22-30. See also reference 9.

9. D.H.R. Barton, G.P. Moss and J.A. Whittle, J. Chem. Soc. (C), 1813 (1968).

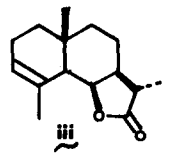
10. In contrast, thioketal i gave ii in excellent (>80%) yield under these conditions[14] :



i ii

11. Cf. P. Crabbé and A. Guzmán, Tetrahedron Letters, 115 (1972).

12. A second non-acidic product tentatively identified as lactone iii was formed in 5-10% yield.



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13. Although various vicinal halides have been used previously with enolates in cyclopropane formation (C. Dupin and R. Fraisse-Jullien, Bull. Soc. Chim. France, 1993 (1964)), coupling (W.G. Kofron and C.R. Hauser, J. Org. Chem., 35, 2085 (1970)), and disubstitution reactions (B. Angelo, C. R. Acad. Sci., C, 273, 1767 (1971)), we are unaware of any reported examples of the formation of isolable α-halocarbonyl compounds in this type of reaction. However, bromination of 1-propenyllithium has been observed (G.M. Whitesides, C.P. Casey and J.K. Krieger, J. Amer. Chem. Soc., 93, 1379 (1971)).

14. Unpublished results from this laboratory.