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LACTONE SYNTHESIS VIA THE INTRAMOLECULAR ALKYLATION OF β-KETO ESTER DIANIONS

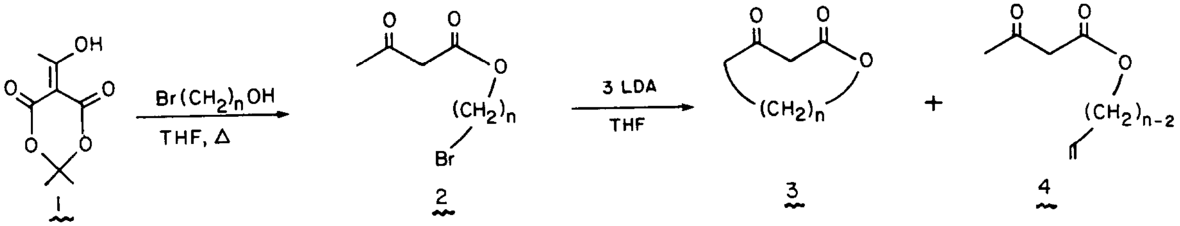
Russell J. Sims, Samuel A. Tischler and Larry Weiler*

Department of Chemistry, University of British Columbia, Vancouver, B.C., Canada V6T 1Y6

Abstract: Long chain ω-halo β-keto esters undergo intramolecular alkylation via the dianions to yield macrocyclic β-keto lactones.

Since the isolation of exaltolide (pentadecanolide) by Kerschbaum[1] fifty-five years ago, a large number of macrocyclic lactones have been isolated from a variety of sources. We were interested in the synthesis of macrocyclic β-keto lactones which are the skeletal subunit in the antiobiotics narbomycin[2] and diplodialide A[3]. Partial reduction of the keto group would give β-hydroxy lactones. Recently two components of the defense secretion of the termite *Armitermes neotenicus* have been identified as very large-ring β-hydroxy lactones[4]. Finally complete reduction of the keto group would give the musk lactones[5].

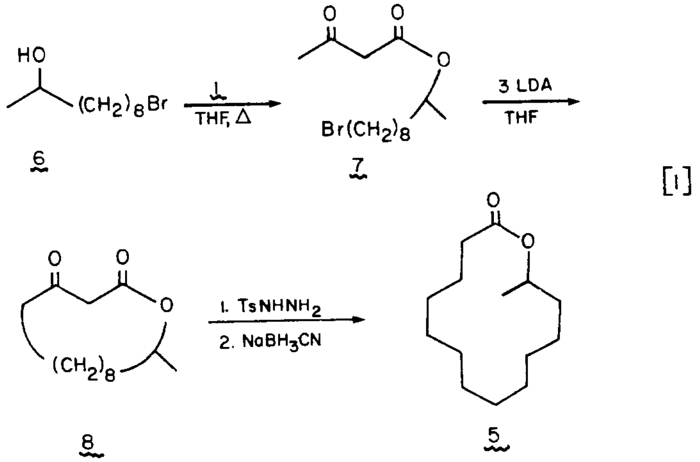
At this time we report our preliminary results on the synthesis of β-keto lactones and on some subsequent reactions of these compounds. Earlier Ireland and Brown[6] had prepared simple macrocyclic β-keto lactones by a modification of the Claisen condensation. Our studies were prompted by a desire to carry out an intramolecular alkylation of the dianion of β-keto esters[7]. Towards this end a series of model compounds **2** for the cyclization were prepared in good yield by heating at reflux a solution of acetyl Meldrum's acid (**1**) and an ω-bromo alcohol in THF[8]. The subsequent dianion generation and intramolecular alkylation was attempted by the dropwise addition of the β-keto ester bromide **2** to a solution of three equivalents of lithium diisopropyl amide in THF at 0°C, then allowing the solution to slowly warm to room temperature. For **2**, $n > 9$, the dianion undergoes cyclization via alkylation at the γ-carbon to give the β-keto lactones **3** in modest yield[9]. For **2** with $n < 8$ the only product isolated was the alkene **4** resulting from elimination. It was easily shown that dianion generation was occurring in these elimination reactions by alkylation with methyl iodide. The elimination in **2**, $n < 8$, may reflect the geometric constraint in the transition state for cyclization arising from the need for the long chain halide to span five successive planar atoms. The ^{1}H-NMR spectra of the β-keto lactones **3** typically contain an unsymmetric triplet ($J \simeq 5$ Hz) at δ 4.25 due to the ω-methylene protons, a singlet at δ 3.45 due to the C_2-protons, and a triplet ($J = 7$ Hz) at δ 2.61 due to the protons on C_4. The mass spectra of the β-keto lactones 3 contain relatively strong peaks due to M^+ and M^+-H_2O ions, the latter being unusual for open chain β-keto esters[10].



n	% yield (2)[a]	% yield (3)[a]	% yield (4)[a]
5	74	0	41
6	86	0	45
7	84	0	57
8	86	0	41
9	95	43	0
10	92	45	0
11	85	49	0

[a] Isolated yields

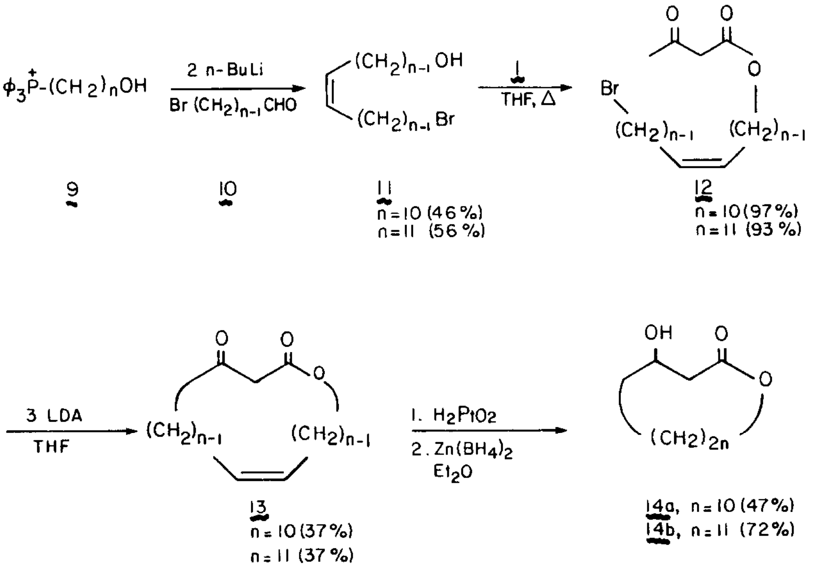
A synthesis of 13-tetradecanolide (5), a musky constituent from *Galbanum* oil[11] is shown in eq. 1. Alcoholysis of acetyl Meldrum's acid (1) with bromoalcohol 6, prepared by sodium borohydride reduction of 10-bromo-2-decanone,[12] gave the β-keto ester 7 in excellent yield. The ester 7 was subsequently cyclized, as above, to give the β-keto lactone 8 in modest yield. The keto group of 8 was converted into its *p*-toleunesulfonyl hydrazone then reduced with sodium cyanoborohydride[13] to give the methyl substituted lactone 5 in good yield. The synthetic sample had spectroscopic and chromatographic properties identical to the natural product. This sequence demonstrates the incorporation of alkyl substituents on the lactone and the facile reduction of the β-keto group.



[1]

Recently Prestwich has reported the isolation of two very large ring β-hydroxy lactones **14a** and **14b** from the defense secretion of the termite *Armitermes neotenicus*[4]. The β-keto lactones were obvious precursors to **14**, however it was not clear if the dianion cyclization could be extended to rings of this size.

Our route to these compounds is shown in eq. 2. Wittig reaction of the dianion from the hydroxy phosphonium salts **9**[14] with the bromoaldehydes **10**[15] afforded the ω-bromoalcohols **11** in moderate yield. Alcoholysis of acetyl Meldrum's acid (**1**) with the bromoalochols **11** gave the β-keto esters **12** in excellent yield. These β-keto esters were cyclized to **13** in moderate yield. Catalytic reduction of the olefin **13** followed by zinc borohydride reduction of the keto group gave the β-hydroxy lactones **14**.



The spectral properties of **14a** and **14b** were consistent with the assigned structures but did show interesting differences. The 400-MHz ^{1}H-NMR spectrum of **14a** displayed a complex multiplet at δ 4.15 due to the C-24 methylene protons. This multiplet collapsed to an AB quartet (J = 12 Hz) on irradiation of the C-23 methylene protons at δ 1.64. The 400-MHz ^{1}H-NMR spectrum of **14b** has a triplet (J = 6 Hz) at δ 4.19 assigned to the C-26 protons. This triplet collapsed to a singlet when the C-25 protons at δ 1.66 were irradiated. Therefore **14a** exists in a conformation such that the asymmetry due to C-3 renders the protons on C-24 magnetically nonequivalent whereas in **14b** the protons on C-26 are magnetically equivalent[16].

References and Notes

1. M. Kerschbaum, *Ber. Deutsch. Chem. Ges.*, **60B**, 902 (1927).
2. R. Corbaz, L. Ettlinger, E. Gaumann, W. Keller, F. Kradolfer, E. Kyburz, L. Neipp, V. Prelog, P. Reusser and H. Zahner, *Helv. Chim. Acta*, **38**, 935 (1955).
3. T. Ishida and K. Wada, *J. Chem. Soc., Chem. Commun.*, 209 (1975).
4. G.D. Prestwich and M.S. Collins, *Tetrahedron Lett.*, **22**, 4587 (1981); G.D. Prestwich, *Tetrahedron*, **38**, 1911 (1982).
5. S. Abe, T. Eto and Y. Tsujito, *Cosmetics and Perfumery*, **88**, 67 (1973).
6. R.E. Ireland and F.R. Brown, Jr., *J. Org. Chem.*, **45**, 1868 (1980).
7. a) S.N. Huckin and L. Weiler, *J. Amer. Chem. Soc.*, **96**, 1082 (1974);
   b) P.E. Sum and L. Weiler, *Can. J. Chem.*, **55**, 996 (1977).
8. Y. Oikawa, K. Sugano and D. Yonemitsu, *J. Org. Chem.*, **43**, 2087 (1978).
9. Efforts to detect and isolate other products in this reaction have been unsuccessful as yet and the material balance is poor. However, these yields are comparable to those reported in ref 6 for similar compounds.
10. L. Weiler, *Can. J. Chem.*, **50**, 2707 (1972).
11. R. Kaiser and D. Lamparsky, *Helv. Chim. Acta*, **61**, 2671 (1978).
12. J. Cason and D.M. Walka, *J. Org. Chem.*, **37**, 669 (1972).
13. R. Baker and R.J. Sims, *Tetrahedron Lett.*, **22**, 161 (1981).
14. M. Horiike, M. Tanouchi and C. Hirano, *Agric. Biol. Chem.*, **49**, 257 (1980).
15. n = 10: P. Chuit, F. Boelsing, J. Hausser and G. Malet, *Helv. Chim. Acta*, **9**, 1074 (1926).
    n = 11: T. Izawa and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **52**, 555 (1979).
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