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REDUCTIVE AMINATION OF α-FORMYL LACTONES. A ROUTE TO α-METHYLENE LACTONES. [1]

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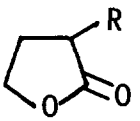
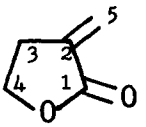
There has been considerable recent interest in the synthesis of α-methylene lactones [2] due to the biological activity (e.g., as tumorstatic or antibiotic agents) of many natural products that contain this structural unit [3]. Although the published syntheses embody a diversity of approaches, their general applicability remains to be ascertained and some have drawbacks, such as low overall yields and rather severe reaction conditions. The recent paper by Grieco and Hiroi [2k] has prompted us to report our development of a new synthetic route to α-methylene-γ and δ-lactones based on the reductive amination of α-formyl lactones.



1, R= H
2, R= =CHOH
3, R= $CH_2N(CH_3)_2$
4, R= $CH_2\overset{\oplus}{N}H(CH_3)_2$ $I^{\ominus}$



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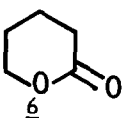

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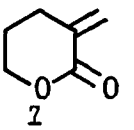

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γ-Butyrolactone (1) was converted to the sodium salt of α-hydroxymethylene-γ-butyrolactone (2) [4a] by reaction with ethyl formate in a diethyl ether suspension of sodium hydride containing a catalytic quantity of absolute ethanol at 30° under nitrogen. The sodium salt of 2 [4b] was reductively aminated with dimethylamine—dimethylamine hydrochloride and sodium cyanohydridoborate at ca pH 10 in anhydrous methanol for 72 to 96 hours at 25° according to the method of Borch et al.[5] to give α-dimethylaminomethyl-γ-butyrolactone (3)+: liquid, 70%

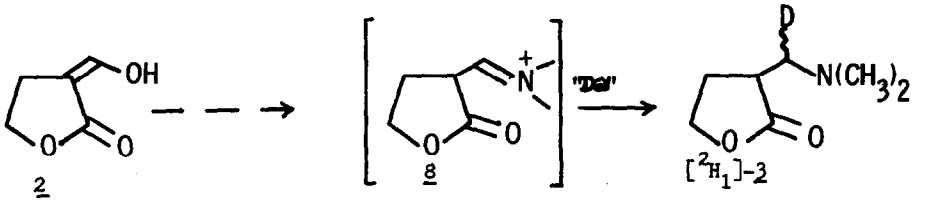
+Satisfactory combustion analyses were obtained for all new compounds.

bp 72-73° @ 0.05 mm; η_D^{25} 1.4565; ν_{max}^{neat} 1770cm^{-1}; nmr ($CDCl_3$-TMS, 60 MHz), ppm, 2.24 (s, 6H), 2.40-2.80(m, 5H), 4.30(m, 2H); hydrochloride, mp 190-190.5°. Conversion of 3 to its methiodide (4) [6] was accomplished quantitatively by treatment with methyl iodide at 25° in methanol. Shake-out of 4 with a mixture of 5% aqueous sodium bicarbonate and methylene chloride at 25° gave the known α-methylene-γ-butyrolactone (5) [7] : liquid, overall yield from 1, 60%; ν_{max}^{neat} 1765, 1668, and 810cm^{-1}; nmr ($CDCl_3$-TMS, 60MHz), ppm, 2.98(m, 2H), 4.37 (t, J=7Hz, 2H), 5.64(t, J=3Hz, 1H), 6.13(t, J=3Hz, 1H); M^+ 98. δ-Valerolactone (6) was taken through the same sequence of reactions to give α-methylene-δ-valerolactone (7) [7b] : liquid, overall yield#, 20%; ν_{max}^{neat} 1730, 1630, 814cm^{-1}; nmr ($CDCl_3$-TMS, 60MHz), ppm, 2.00 (m, 2H), 2.71 (m, 2H), 4.38(t, J=7Hz, 2H), 5.57(dd, $J_{AB}=J_{A'B'}$, 1Hz, 1H), 6.40(dd, $J_{AB}=J_{A'B'}$, 1Hz, 1H); M^+ 112.

As several of the heretofore reported syntheses of α-methylenelactones were not successful when directed towards the synthesis of α-methylene-δ-lactones, the preparation of 7 is indicative of the potential general utility of the α-methylene lactone synthesis reported herein, which complements the route to such compounds described by Grieco and Hiroi. We are exploring the scope of our synthesis, the results of which will be reported in the full paper.

Since studies of the bioorganic chemistry of α-methylene lactones would be facilitated by isotopic labelling of such compounds, we have briefly explored this using 5 as a model compound. Repetition of the reaction sequence from 2 using [^{2}H]-$NaCNBH_3$ [5] gave [^{2}H]-5(99%d_1).

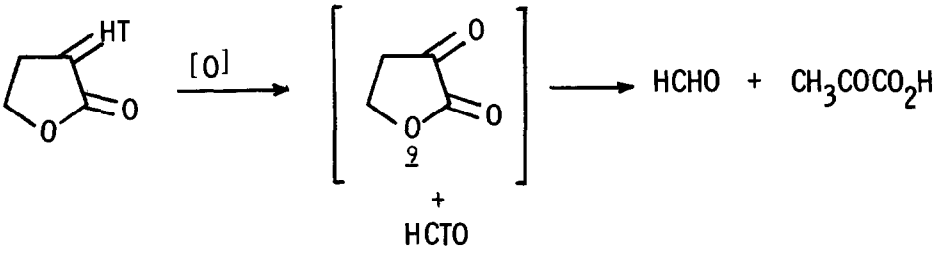
Scheme I



Yield from one run only.

Relative integration of the signals for the C-5 vinylic protons indicated 45-50% regiospecific introduction of ^{2}H, in accord with the mechanism for reductive amination described by Borch et al.[5] (Scheme I). Exact repetition of the reaction sequence using [^{3}H]-$NaCNBH_3$ [5] gave [^{3}H]-5 (5.90×10^5 dpm/mmole, counted as its Michael adduct with L-cysteine [8]), which contained only 85% of the specific radioactivity of [^{3}H]-3 (6.93×10^5 dpm/mmole, counted as its hydrochloride), indicative of base-catalysed tritium exchange of the α-proton in 3. However, both Lemieux-Johnson oxidation [9] and non-catalytic OsO_4-$NaIO_4$ cleavage [10] of [^{3}H]-5 gave [^{3}H]-HCHO (3.59×10^5 dpm/mmole, 4.35×10^5dpm/mmole, respectively, isolated and counted as its dimethone) containing only 61% and 74% of the specific radioactivity of [^{3}H]-5. These results can be explained by Scheme II whence radioinactive HCHO would be expected to arise

Scheme II



from C-4 of [^{3}H]-5 via retroaldol fragmentation of 9 [11]. Apparently the "rates" of generation of [^{3}H]-HCHO and [^{1}H]-HCHO from [^{3}H]-5 differ such that the r.m.a. of the [^{3}H]-HCHO dimethone lay between 50%, the expected value had two molar equivalents of HCHO arisen simultaneously during the oxidative cleavage of [^{3}H]-5, and 100%, the expected value for one equivalent of HCHO solely from C-5 of 5. We do not feel these results should detract from the possibility of isotopic labelling of α-methylene lactones by judicious application of our synthetic route, as the choice of 5 as our model compound simply was an unfortunate one.

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8. Prepared by the addition of an ethanolic solution of 5 to a warm aqueous solution of L-cysteine: mp 199-200°.

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10. One equivalent of OsO_4 was used to form the diol of 5, which was isolated and cleaved with $NaIO_4$.

11. This proposed fragmentation may very well explain the lack of success we have had in several attempts to synthesize 9, both by the reported method [12] and from formaldehyde and pyruvic acid. However, 9 and its hydrolysis product, 2-keto-4-hydroxy butyric acid, have been prepared by the reaction of homoserine with pyridoxal in the presence of Cu^{2+} ions [13].

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