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SONOCHEMICAL ACCELERATION OF CONVERSION OF 2-ALKOXYTETRAHYDROFURANS TO γ-BUTYROLACTONES SYNTHESIS OF (±)-QUERCUS LACTONE-A

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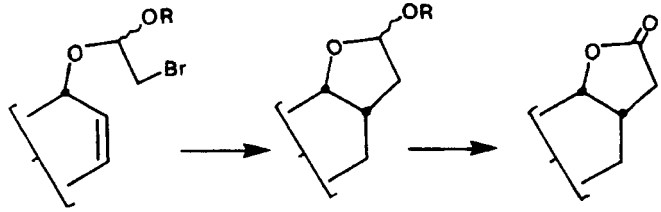
***ABSTRACT**: Effect of sonochemical irradiation on the conversion of 2-alkoxytetrahydrofurans to γ-butyrolactones by Jones reagent, and its extension to the highly stereoselective synthesis of quercus lactone a, is reported.*

Butyrolactones are found ubiquitously throughout organic and natural product chemistry, as they are useful synthetic intermediates for a variety of functional moieties.[1] Last decade has witnessed a rapid growth in the use of radical cylisation reaction in organic synthesis.[2] Radical cyclisation[3-5] of mixed α-bromo acetals of allyl alcohols provides a very convenient and useful method, quite often with high degree of regio and stereoselectivity, for the construction of 2-alkoxytetrahydrofurans, e.g. 1—>2. Conversion of 2-alkoxytetrahydrofuran to γ-butyrolactones (2—>3) can be achieved either by stepwise i.e., hydrolysis followed by oxidation,[6] or in a single

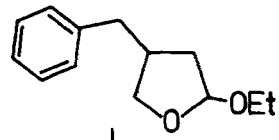
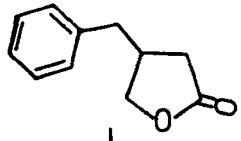
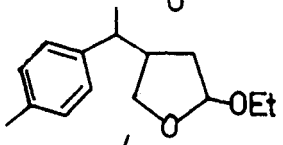
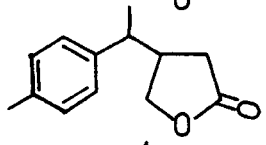
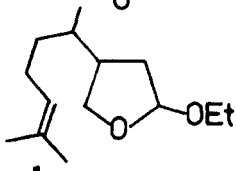
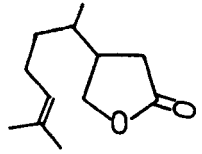
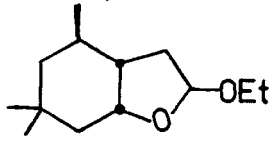
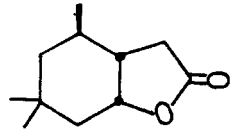
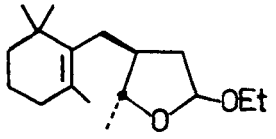
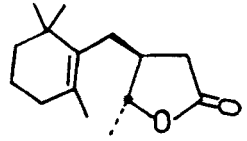
step using standard Jones reagent.[5] In the latter case, the efficiency depends on the rate of hydrolysis, and the stability of the final compound under acidic conditions. Usually it takes about one to several hours depending on the nature of the alkoxy group and yields are, in general moderate to good. The use sonochemical methods in rapid organic synthesis[7] is of contemporary interest. Herein we report the effect of ultrasound on the transformation 2—>3, which not only accelerated but also improved the efficiency, and its extention to a highly stereoselective synthesis of (±)-quercus lactone-a.



1 2 3

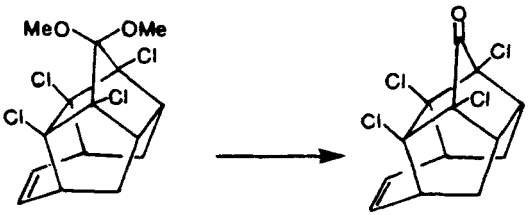
2-Alkoxytetrahydrofurans 2a-e were obtained in very good yield by radical cyclisation (RC) of bromo acetals 1a-e using *in situ* generated[4,8] catalytic tri-n-butyltin hydride ($^{n}Bu_3SnCl/NaCNBH_3/t\text{-}BuOH$) in the presence of a catalytic amount of azobisisobutyronitrile (AIBN). Sonochemical irradiation of a mixture of hemiacetal 2 in acetone and two to three equivalents of 1.6M Jones reagent for two to three minutes resulted in the formation of γ-butyrolactones 3a-e in very good yields (TABLE 1).[9] As the Jones oxidation is known to be very fast, it is obvious that in the present conversion, ultra sound is

Table 1. Synthesis of γ-butyrolactones[a]

entry	hemiacetal 2	butyrolactone 3	Yield[b] (%)
a			80
b			83[c]
c			80[c]
d			84
e			93[d]

a. All the compounds reported here exhibited satisfactory spectral data, consistent with their structures.
b. Yields refer to unoptimised, isolated and chromatographically pure lactones.
c. 1:1 Mixture of diastereoisomers.
d. The amount of other stereoisomer is <5% by NMR.

accelerating the hydrolysis step. To test this hypothesis, hydrolysis of α,α'-dichloro acetal 4 (acetals known for their very slow hydrolysis)[10] was investigated. Thus, sonochemical irradiation of a mixture of the acetal 4 in



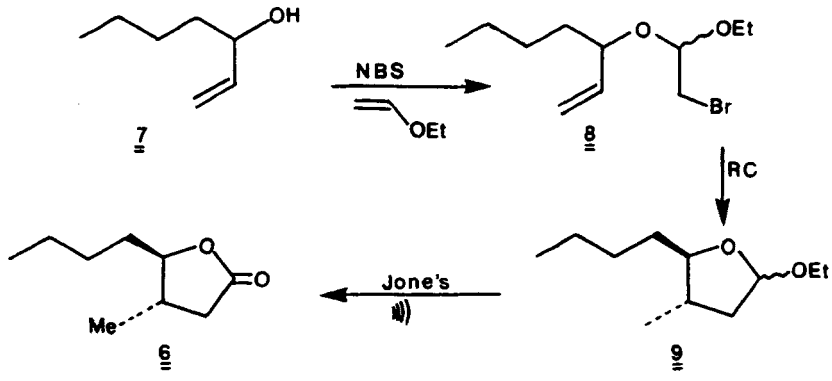
4 5

methylene chloride and 90% aqueous H_2SO_4 for 4 min furnished the ketone 5, m.p. 280 °C (lit.[10] 281-282 °C) in almost quantitative yield supporting our hypothesis.

SYNTHESIS OF QUERCUS LACTONE-A:

Quercus lactone-a (6) along with its *cis*- isomer b was isolated from the wood of three *Quercus* species.[11] Interestingly these lactones were also detected as ingredients of aged (in oak barrels) wines and spirits. The *trans* configuration of the butyl and methyl groups has been established by ^1H NMR spectroscopy, and the absolute stereochemistry on the basis of emperical correlation.[11] We have developed a highly stereoselective synthesis of quercus lactone-a starting from hex-1-en-3-ol (7), using radical cyclisation reaction and sonochemically accelerated Jone's oxidation as key reactions.

The requisite starting allyl alcohol 7 was obtained by a 1,2-addition of n-butyllithium to acrolein. The key radical precursor, bromo acetal 8 (mixture of diastereoisomers), was obtained in 78% yield, by a low temperature



7 8 9 6

bromination of ethyl vinyl ether using N-bromosuccinimide (NBS) in the presence of the alcohol 7. Refluxing a 0.2M t-butanol solution of the bromo acetal 8 with $^{n}Bu_3SnCl$ (0.1 equiv.) and $NaCNBH_3$ (1.5 equiv.) in the presence of a catalytic amount of AIBN for one hour,[4,8] furnished the cyclised product 9, with high degree of stereoselectivity, in 78% yield. Conversion of the hemiacetal 9 to the quercus lactone-a was achieved, in 97% yield, by the ultra sound accelerated Jone's oxidation. The synthetic material exhibited the spectral data (IR, ^{1}H and ^{13}C NMR) identical to that reported in the literature.[6,12] In line with the expected *trans* preference in the cyclisation of 4-substituted hexenyl radicals,[2] the other stereoisomer, quercus lactone-b, was found to be <<5% by NMR.

In conclusion, we have described here the improved and rapid conversion of 2-alkoxytetrahydrofurans to γ-butyrolactones by Jone's reagent, using sonochemistry to accelerate the hydrolysis of hemiacetal to lactol.

EXPERIMENTAL SECTION

Infrared spectra were recorded on a Hitachi 270-50 spectrophotometer. ^{1}H (90 MHz) and ^{13}C NMR (22.5 MHz) spectra were recorded on a Jeol FX-90Q spectrometer using $CDCl_3$ as solvent, and the chemical shift (δ ppm), and coupling constants (Hz) are reported in standard fashion with reference to internal tetramethylsilane (^{1}H NMR) or the central line (77.1 ppm) of $CDCl_3$ (^{13}C NMR). Sonochemical experiments were carried out using a Toshinwal SW-7.5 ultrasonic cleaning bath. Acme's silica gel (100-200 mesh) and Qualigen's neutral alumina were used for column chromatography. AIBN was crystallised from methanol and stored in dark. CH_2Cl_2 was dried and distilled over P_2O_5. t-Butanol was distilled over sodium. $^{n}Bu_3SnCl$, $NaCNBH_3$ and n-BuLi were obtained from Fluka and used as such. All the starting materials and 1.6M Jone's reagent were prepared using the standard procedures.

2,3,4,6-Tetrachloropentacyclo[5.5.1.$O^{2,6}$.$O^{3,10}$.$O^{4,8}$]trideca-11-en-5-one (5):

To a methylene chloride (5 ml) solution of the acetal **4** (122 mg, 0.32 mmol) was added 90% aqueous sulfuric acid (2 ml) and the reaction mixture was sonicated for four minutes. The reaction mixture was diluted with water (5 ml) and the solid ketone **5** separated out was filtered using a sintered funnel. The solid was washed with water, methylene chloride and dried (100 mg, 94%). m.p. 280 °C (lit.[10] 281-282 °C). IR (nujol): ν_{max} 1800 cm^{-1}.

Quercus lactone-a (6):

To a cold (-50 °C), magnetically stirred solution of the alcohol **7** (460 mg, 4 mmol) and ethyl vinyl ether (0.6 ml, 6 mmol) in dry methylene chloride (10 ml) was added a methylene chloride solution (20 ml) of NBS (1.3 g, 7 mmol) over a period of 20 min. The reaction mixture was stirred and allowed to warm up to room temperature over

a period of 45 min. The reaction mixture was diluted with methylene chloride, washed with 2% aqueous NaOH, water and brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of residue over neutral alumina (20 g) using ethyl acetate-hexane (1:20) as eluent furnished the bromo acetal 8 (1:1 mixture of diastereoisomers, 850 mg, 78%) as an oil. [IR (neat): ν_{max} 1195, 1115, 1025, 925 cm^{-1}. ^1H NMR : δ 5.4-6.0 (1 H, m) and 5.0-5.4 (2 H, m) (olefinic), 4.68 (1 H, 2xt, J=7 Hz, O-CH-O), 3.3-4.2 (3 H, m, O-CH and $O-CH_2$), 3.35 (2 H, 2xd, J=7 Hz, CH_2Br), 1.05-1.8 (9 H, m), 0.9 (3 H, distorted t, CH_3)].

A solution of the bromo acetal 8 (530 mg, 2 mmol), $^nBu_3SnCl$ (0.08 ml, 0.22 mmol), $NaCNBH_3$ (190 mg, 3 mmol) and AIBN (catalytic) in t-BuOH (10 ml) was refluxed for one hour. The reaction mixture was diluted with ether (50 ml), washed with water, brine and dried (Na_2SO_4). Evaporation of the solvent and purification of residue over silica gel (15 g) column using methylene chloride-hexane (1:2) as eluent furnished the hemiacetal 9 (mixture of diastereoisomers, 297 mg, 80%). [IR (neat): ν_{max} 1195, 1107, 933 cm^{-1}. ^1H NMR: δ 4.9-5.2 (1 H, m, O-CH-O), 3.1-4.0 (3 H, m, O-CH and $O-CH_2$), 0.7-2.5 (18 H, m)]

A solution of the hemiacetal 9 (200 mg, 1.07 mmol) and 1.6M Jone's reagent (2 ml, 3.2 mmol) in acetone (2 ml) was sonicated for three minutes, and 1 ml of isopropanol was added to destroy the excess reagent. The reaction mixture was diluted with ether (15 ml), washed with water, saturated aqueous $NaHCO_3$ and brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of residue over a silica gel (5 g) column using methylene chloride-hexane (1:2) as eluent furnished the Quercus lactone-a (6, 162 mg, 97%) as an oil. IR (neat): ν_{max} 1780, 1465, 1210, 1170 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 4.0 (1 H, q, J=7 Hz), 2.7 (1 H, dd, J=18, 10 Hz), 2.0-2.4 (2

H, m), 1.2-1.9 (6 H, m), 1.14 (3 H, d, J=7 Hz), 0.92 (3 H, distorted t). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 175.9, 86.7, 36.6, 35.6, 33.2, 27.5, 22.1, 16.9, 13.4.

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