A Highly Efficient and Convenient Lactonization Procedure for Strained *trans*-Fused Lactones

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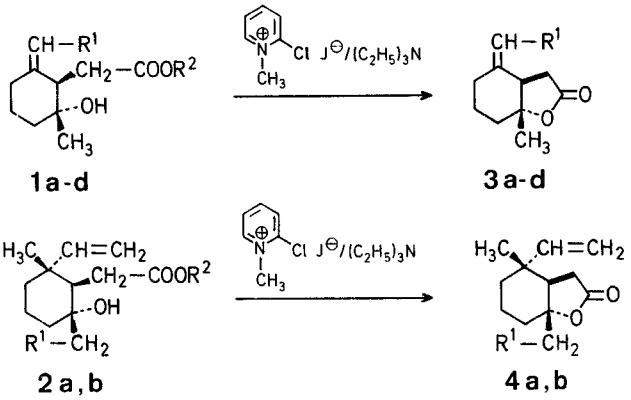
Of the various synthetic routes available for the construction of small-ring lactones, cyclization of the corresponding hydroxy acids remains the most general and expedient route. Thus, δ-lactones[1] as well as monocyclic and *cis*-fused bicyclic γ-lactones are readily formed by essentially spontaneous cyclization of the respective hydroxy acids in the presence of acid, whereas in the case of the more strained, *trans*-fused bicyclic γ-lactones, heating of the hydroxy acid under acidic conditions[2] or treatment with *N,N'*-dicyclohexylcarbodiimide[3] may be required. When the hydroxy function is tertiary, however, competitive dehydration is a major problem.

The purpose of this report is to call attention to an apparently overlooked but highly efficient general method for the lactonization of *trans*-γ-hydroxy acids mediated by 2-chloro-1-methylpyridinium iodide in the presence of triethylamine. The latter reagent system[4] has found useful application in the esterification of carboxylic acids[5] and, in one report, the lactonization of unsubstituted ω-hydroxy acids, using a high-dilution technique[6].

As part of an effort directed towards a stereoselective synthesis of 4,4-disubstituted-*trans*-7a-methyl-2(3*H*)-hexahydrobenzofuranone systems, we have examined the lactonization of alkylidenehydroxy acids **1a–d** (R^2 = H) as well as other γ-hydroxy acids including **2a** and **2b**.

Attempted cyclization of methylenehydroxy acid **1a** or its ester (R^2 = *t*-butyl) by heating with or without an acid catalyst afforded only dehydration and polycondensation products. Treatment of **1a** or the methoxyethoxymethyl protected derivative of **1c** with *N,N'*-dicyclohexylcarbodiimide and pyridine gave similar results with less than 10% of the corresponding lactones **3** detected. By contract, **1a** is converted to its lactone



3a in 97% yield by treatment with excess 2-chloro-1-methylpyridinium iodide and triethylamine in refluxing dichloromethane. In identical fashion, the acid-sensitive hydroxy acids **1b–d**, **2a**, and **2b** were transformed into their respective lactones **3b–d**, **4a**, and **4b** and isolated in yields of 95% or greater (Table 1).

The examples cited above and in Table 1 are representative of the many successful *trans*-γ-lactonizations achieved in our laboratory by the 2-chloropyridinium method. In all cases the yields are nearly quantitative. Interestingly, alternative lactonization of hydroxy acids **1** in the presence of 2,2'-dipyridyl disulfide/triphenylphosphine, Mukaiyama's reagent[7] which has been successfully applied to macrolide synthesis[8], generally led to much lower yields of the corresponding lactones **3**.

Hydroxy acids **1a–d** (R^2 = H) (Table 2) were obtained by saponification of the corresponding *t*-butyl esters **1a–d** (R^2 = *t*-butyl). These esters were in turn obtained by the previously reported regioselective *trans*-addition of *t*-butoxycarbonylmethyl-diethyl-alane to the corresponding alkylideneoxiranes[9]. The preparation of hydroxy acid **2a** has been previously reported[3], whereas **2b** is available by Raney-Nickel deselenation of the related hydroxy acid **2** (R^1 = Se—C_6H_5) prepared in an analogous fashion to **2a**[10].

Table 1. Lactones **3** and **4** Obtained by the 2-Chloro-1-methylpyridinium Iodide/Triethylamine Method

Lactone	R^1	Yield [%]	m.p. [°C]	Molecular[a] Formula or Lit. m.p.	I.R. (film)[b] ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm][c]
3a	H	97	35–37°	$C_{10}H_{14}O_2$ (166.2)	1660, 1780	1.17 (s, 3H); 1.6–2.7 (m, 9H); 4.65 (br. s, 1H); 4.93 (br. s, 1H)
3b	$CH_2Si(CH_3)_3$	99	oil	$C_{14}H_{24}O_2Si$ (252.4)	1675, 1780	0.02 (s, 9H); 1.23 (s, 3H); 1.45 (d, J=9 Hz, 2H); 1.5–3.4 (m, 9H); 5.35 (br. t, J=9 Hz, 1H)
3c	CH_2OH	98	oil	$C_{11}H_{16}O_3$ (196.2)	1775, 3445	1.27 (s, 3H); 1.4–2.85 (m, 10H); 4.15 (d, J=7 Hz, 2H); 5.67 (t, J=7 Hz, 1H)
3d	$CH_2OCH_2SCH_3$	95	oil	$C_{13}H_{20}O_3S$ (256.4)	1680, 1785	1.25 (s, 3H); 2.17 (s, 3H); 1.7–2.9 (m, 9H); 4.08 (d, J=7 Hz, 2H); 4.68 (s, 2H); 5.63 (t, J=7 Hz, 1H)
4a	SC_6H_5	95[d]	oil	$C_{18}H_{22}O_2S$ (302.4)	1787	1.11 (s, 3H); 1.3–2.2 (m, 6H); 2.2–2.75 (m, 3H); 3.36 (s, 2H); 4.8–6.0 (m, 3H); 7.1–7.6 (m, 5H)
4b	H	96[d]	oil	$C_{12}H_{18}O_2$ (194.3)	see Ref.[10]	see Ref.[10]

[a] Satisfactory microanalyses were obtained (C, ±0.10; H, ±0.06) for compounds **3a**, **3b**, **3d**, **4a**, and **4b**; analyses performed by Atlantic Microlab., Inc. Liquid and highly hygroscopic compound **3c** was uniform on T.L.C. and gave good high resolution M.S. data for the molecular ion.

[b] Perkin-Elmer 283B spectrophotometer.

[c] Varian EM-360 spectrometer.

[d] A 78% yield was obtained by the *N,N'*-dicyclohexylcarbodiimide/pyridine method[3,10].

Table 2. Characteristics of Hydroxy Acids **1a–d** ($R^2 = H$)

Hydroxy Acid	R^1	Yield [%]	m.p.[a] [°C]	Molecular[b] Formula	^{1}H-N.M.R.[c] δ [ppm]
1a	H	93	127–129°	$C_{10}H_{16}O_3$ (184.2)	1.08 (s, 3H); 1.2–2.9 (m, 9H); 4.73 (s, 1H); 4.89 (s, 1H); 5.15 (br. s, 2H)
1b[d]	$CH_2Si(CH_3)_3$	85	141–142°	$C_{14}H_{26}O_3Si$ (270.4)	0.04 (s, 9H); 1.25 (s, 3H); 1.4–3.4 (m, 11H); 5.53 (br. t, J=8 Hz, 1H); 5.8 (br. s, 2H)
1c[e]	CH_2OH	63	154–156°	$C_{11}H_{18}O_4$ (214.3)	1.05 (s, 3H); 1.1–3.0 (m, 12H); 3.95 (m, 2H); 5.33 (t, J=6 Hz, 1H)
1d[e]	$CH_2OCH_2SCH_3$	84	92–93°	$C_{13}H_{22}O_4S$ (274.4)	1.27 (s, 3H); 1.6 (m, 5H); 2.18 (s, 3H); 2.3–4.6 (m, 6H); 4.68 (s, 2H); 5.70 (t, J=7 Hz, 1H); 6.40 (br. s, 2H)

[a] Compounds crystallized from diethyl ether/hexane.
[b] Satisfactory microanalyses were obtained (C, ±0.16; H, ±0.02).
[c] Spectra of compounds **1a**, **1b**, and **1d** taken in $CDCl_3$, and of compound **1c** in DMSO-d_6 with TMS as an internal reference; Varian EM-360 spectrometer.
[d] Tentatively assigned the (*Z*)-configuration.
[e] (*Z*)-Configuration.

Hydroxy Carboxylic Acids 1a–d; General Procedure:
A solution prepared from ethanol (20 ml), potassium hydroxide (85%, 0.26 g, 4 mmol), and *t*-butyl ester **1** (1 mmol) is heated at 50 °C for 30 h under an argon atmosphere. Concentration on an evaporator is followed by dilution with ice/water (3 ml), acidification to pH 2–4 with cold 1 normal hydrochloric acid, and extraction with diethyl ether (5 × 50 ml). The combined extracts are washed with saturated sodium chloride solution (10 ml), dried with sodium sulfate, and concentrated. The deposited hydroxy acid **1** is recrystallized from diethyl ether/hexane. Yields, m.p.s, and spectral data are provided in Table 2.

Lactones 3 and 4; General Procedure:
To 2-chloro-1-methylpyridinium iodide (1.0 g, 4 mmol) in dry dichloromethane (40 ml) under an argon atmosphere, a solution of hydroxy acid **1** (1 mmol) and triethylamine (1.1 ml, 8 mmol) in dichloromethane (20 ml) is added and the resultant mixture is heated under reflux for 15 h. Dichloromethane is evaporated and the residue is extracted with pentane (5 × 60 ml). The extract is concentrated and the lactone is isolated by flash chromatography on silica gel, eluting typically with 90 : 10 hexanes/ether mixture. Yields and spectral data are provided in Table 1.

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