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A δ-LACTONE SYNTHESIS INVOLVING AN INTRAMOLECULAR 1,4-ADDITION OF α-IODOACETATES TO ENONES

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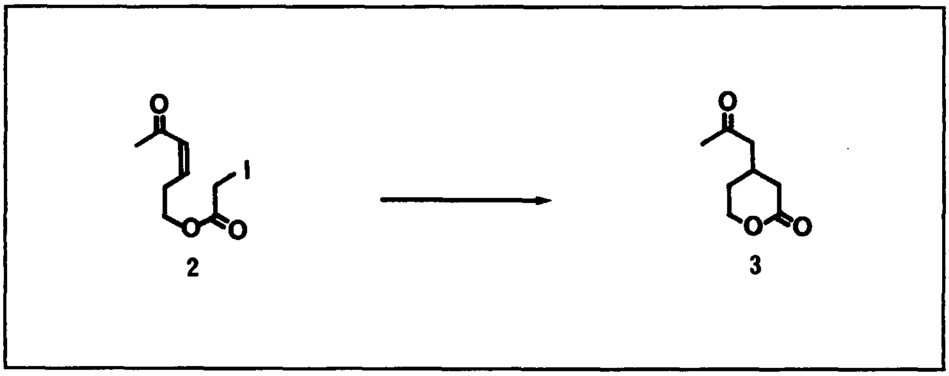
Abstract. A cyclization of δ-(iodoacetoxy)-α,β-unsaturated ketones using iodotrimethylsilane involved a selective 1,4-addition of the acetate subunit to the enone and furnished δ-lactones in good yield.

In connection with work on the synthesis of quassinoids[1,2] such as similikalactone D (1), we required a procedure for the introduction of the δ-lactone ring. Relatively few synthetic procedures are available for the construction of the α,β-carbon-carbon bond[3] in a δ-lactone, and we reported[4] a single example of a successful ring closure of this type in which iodotrimethylsilane (Me_3SiI) induced the cyclization of an α-iodoester 2 to a δ-lactone 3. We now report the results on the scope and mechanism of this lactonization procedure.

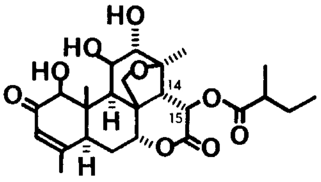


In an effort to effect the cyclization of the α-iodoacetate 2f to the desired δ-lactone 3f (Table 1), we first examined the traditional reagents for the Reformatsky reaction: Zn, Zn(Hg), and Mg, but we recovered only unreacted 2f. We ultimately found that Me_3SiI effected the desired cyclization of 2f to 3f in 96% yield.[4] We favored a mechanism for this process which involved the initial activation of the α-iodoacetate as the

O-trimethylsilyl ketene acetal based on the ^{13}C NMR (CD_3CN, 0°C, δ 83.3, $\underline{C}H_2$=C with concomitant disappearance of a signal at δ 168.8, $\underline{C}OCH_2I$) of a model system, phenyl α-iodoacetate exposed to Me_3SiI. We have not, however, directly observed ketene acetals such as 4a in the cyclization of the α-iodoacetate 2a, and we noted that the model system was converted slowly to the ketene acetal at the temperature (-20°C) where the cyclizations in Table 1 were typically conducted. Consequently, the suggestion that the cyclization process involved a ketene acetal intermediate must be regarded as tentative. Based on the precedented addition of Me_3SiI to enones[5], we also favored a subsequent step involving an addition of Me_3SiI to the enone portion of 2 or the activation of the enone by Me_3SiI as displayed in structure 5a. The failure of Et_3SiI to add to enones such as 2-cycloheptenone, which readily react with Me_3SiI, was consistent with our observation that neither Et_3SiI or t-$BuMe_2SiI$ would promote the lactonization of 2f under conditions where Me_3SiI afforded excellent yields of 3f. Also consistent with the addition of Me_3SiI to the enone was the observation of the O-trimethylsilyl enol ether 6a in the lactonization of 2a [^{1}H NMR (CD_3CN, -20°C, as a 1:4 mixture of E:Z-isomers) δ 0.18 and 0.32 (two s, $Si(CH_3)_3$), 1.94 and 1.98 (two s, vinylic CH_3), 4.61 and 4.71 (two d, vinylic H)]. Finally, the addition of Et_3N in order to scavenge for HI led to good yields of the δ-lactone and excluded the possibility that adventitious HI was the causative reagent in the lactonization process.

Other examples of the cyclization of α-iodoacetates to δ-lactones appear in Table 1.[6] With regard to our quassinoid interests, it was important to establish the compatibility of this cyclization process with substituents located α or α' to the enone functionality. We noted that the cyclization failed in the presence of either a C-13 methyl or C-11β bromo group but succeeded in the presence of a C-11β acetoxy group or C-9,11 double bond. The competitive cyclization of the α-iodoacetate to the C-9 position in 2j was not observed. Limited studies including the cyclization of 2k suggested that this process was not necessarily restricted to the preparation of δ-lactones.

The following is a typical experimental procedure. To 522 mg (1.3 mmol) of 2c in 2.5 mL of anhydrous acetonitrile at -20°C under a nitrogen atmosphere was added 1.04 g (5.2 mmol) of iodotrimethylsilane. A dark brown color was immediately noted. The mixture was stirred for 3 h at -20°C and quenched with 4 mL of 1 M hydrochloric acid solution. The product was diluted with ethyl acetate, washed successively with 0.5 M $Na_2S_2O_3$ solution and brine, and dried over anhydrous $MgSO_4$. The product was chromatographed on silica gel in 1:1 ethyl acetate-hexane to afford 345 mg (100%) of 3c: mp 92.5-93°C (ether); IR (KBr) 1765, 1670, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.88 (d, J=5 Hz, 2, CH_2), 3.25 (dd, J=5 and 6 Hz, 2, C-3 CH_2), 3.83 (m, 1, CH), 6.96-7.98 (m, 9, aromatic H); exact mass spectrum calcd for $C_{17}H_{14}O_3$, 266.0943, found 266.0941.



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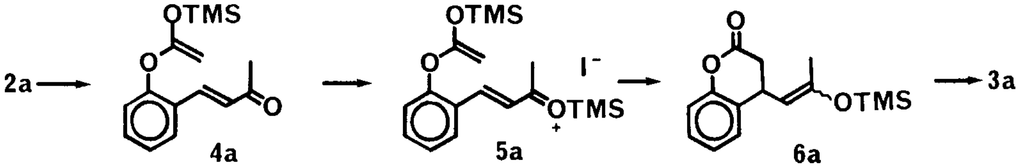

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1. This paper is the fourth in a series dealing with the synthesis of quassinoids. For the third paper, see N. K. Dunlap, M. R. Sabol, and D. S. Watt, Tetrahedron Lett., 25, 5839 (1984).

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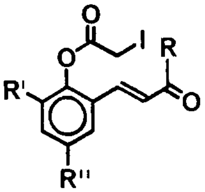
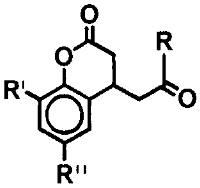
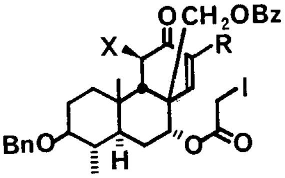
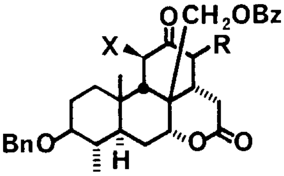
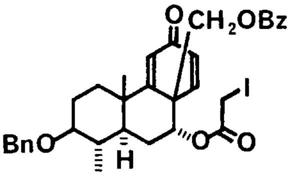
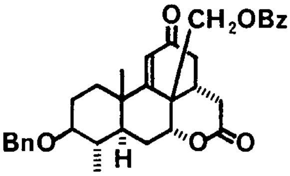
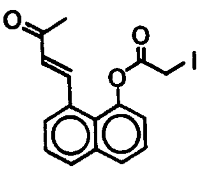
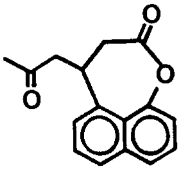
6. All new compounds had infrared, NMR, and exact mass spectral and/or combustion analysis data in accord with assigned structures.

Table 1. Synthesis of δ-Lactones 3 from α-Iodoacetates 2 Using Me_3SiI.

	α-Iodoacetate 2	Conditions[a]	Product	Yield (%)
				
a	R = Me R'= H R" = H	2.5 h		79%
b	R = Et R'= H R" = H	2.5 h		76%
c	R = Ph R'= H R" = H	3 h		100%
d	R = Me R'= H R" = NO_2	2.5 h		0%
e	R = Ph R'= OCH_3 R" = H	3 h		99%
				
f	R = H X = H	3 h		96%
g	R = Me X = OAc	1.75 h[b]		0%
h	R = H X = Br	2 h[b]		0%
i	R = H X = OAc	1.75 h[b]		65%
j				75%
k				25%

a, Me_3SiI (2 equiv), CH_3CN, -20°C; b, in the presence of 1 equiv of Et_3N

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