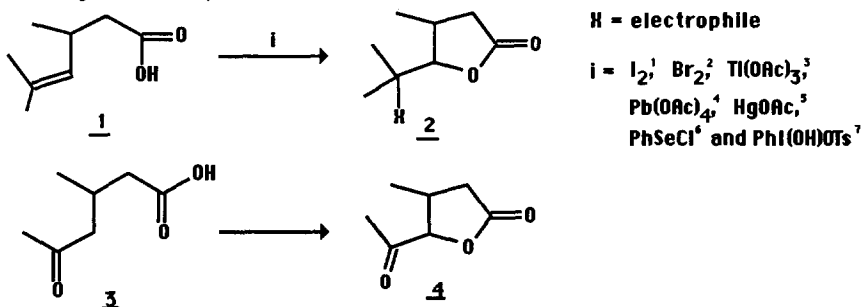


**HYPERVALENT IODINE OXIDATION OF 5-KETO ACIDS AND 4,6-DIKETO ACIDS WITH
[HYDROXY(TOSYLOXY)IODO]BENZENE: SYNTHESIS OF KETO- γ -LACTONES AND DIKETO- δ -
LACTONES**

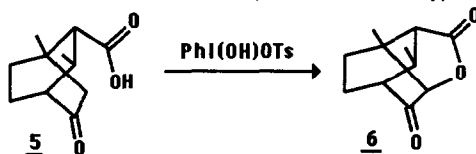
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Hypervalent iodine oxidation of 5-ketoacids, using [hydroxy(tosyloxy)iodo]benzene in dichloromethane under refluxing conditions yielded keto- γ -lactones. Oxidation of 4,6-diketoacids with [hydroxy(tosyloxy)iodo]benzene at room temperature afforded the corresponding diketo- δ -lactones.

Intramolecular cyclization of the type $1 \rightarrow 2$ is a familiar process in organic synthesis and is observed in a very wide range of electrophilic reactions.¹⁻⁷

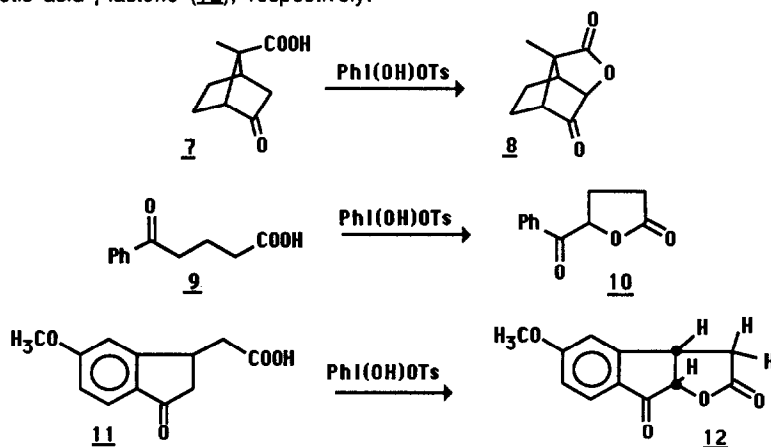


Process $3 \rightarrow 4$ in which creation of an electrophilic center adjacent the carbonyl group initiates the intramolecular nucleophilic cyclization is a logical analog of this type lactonization. Since α -functionalization of the carbonyl group using [hydroxy(tosyloxy)iodo]benzene⁸ involves introduction of a hypervalent iodine center adjacent to the carbonyl group which then undergoes intermolecular displacement, we reasoned that intramolecular participation by a neighboring nucleophilic group might occur. We report now that this is indeed the case and the reaction offers a useful route to γ -ketolactones. A typical example is $5 \rightarrow 6$.

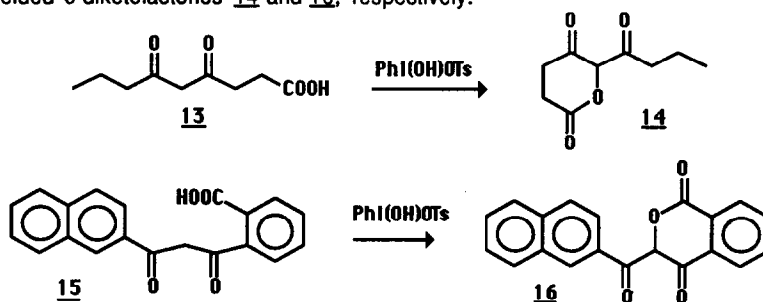


In this case, 1,3-dimethyl-5-oxobicyclo[2.2.2]octane 2-carboxylic acid (**5**)⁹ (1.96 g, 0.10 mole) was dissolved in 100 ml of dry CH₂Cl₂. [Hydroxy(tosyloxy)iodo]benzene (3.92 g, 0.10 mole) was added with stirring and the resulting slurry heated at reflux for 15 hours. The homogeneous solution was cooled to room temperature and washed with cold NaHCO₃ solution. The dichloromethane layer was separated and dried over anhydrous MgSO₄, filtered and the solvent was removed under vacuum. The resulting oil containing ketolactone (**6**) and iodobenzene was chromatographed upon neutral alumina and dichloromethane : hexane (1:9) was used as eluent. Ketolactone (**6**) thus obtained is listed in Table 1 along with its physical data.

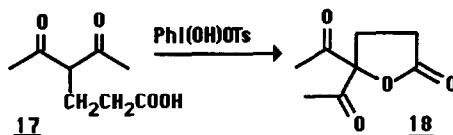
Similarly, 2-keto-7-carboxy-7-methylbicyclo[2.2.1]heptane (**7**),¹⁰ 4-benzoylbutyric acid (**9**)¹⁵ and 5-methoxy-1-indanone-3-acetic acid (**11**)¹¹ yield 2-hydroxy-7-methyl-3-oxo-7-norbornane carboxylic acid- γ -lactone (**8**), 5-benzoyldihydro-2(3*H*)-furanone (**10**) and 2-hydroxy-5-methoxy-3-oxo indane acetic acid- γ -lactone (**12**), respectively.



Further, diketo acids (**13** and **14**)¹² upon reaction with C₆H₅I(OH)OTs in dichloromethane at room temperature, yielded δ -diketolactones **14** and **16**, respectively.



Oxidative cyclization of **17**¹³ with C₆H₅I(OH)OTs / CH₂Cl₂ yielded **18** in reasonable yield.



Similarly, the synthesis of spiro lactone **20** was achieved by the oxidation of **19**¹⁴ with PhI(OH)OTs / CH₂Cl₂ at room temperature.

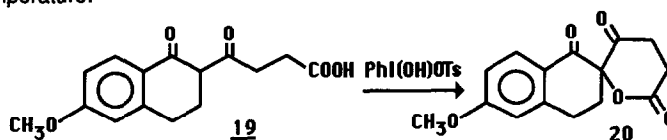


Table 1 Ketolactones Obtained by Oxidation of the Corresponding Ketoacids with PhI(OH)OTs

Product	Yield(%)	m.p.[Lit.m.p.]°C	IR (CDCl ₃)	¹ HNMR (CDCl ₃ ,δ)
6	81	oil ^{1,2}	1794(lactone C=O) 1723(ketone C=O)	1.10(s,3H,CH ₃),1.20(d,3H,CH ₃),1.60(m,2H,2XCH),1.80(m,2H,2XCH), 2.00(d,CH),2.10-2.35(m,2H,2XCH), 4.0(s,OCHCO).
8	76	165-166 ^{1,2}	1790(lactone C=O) 1767(ketone C=O)	1.40(s,3H,CH ₃), 1.70(m,CH), 1.90(m,CH), 2.00(m,CH),2.30(m,CH),2.50(m,CH),3.00(m, COCH), 4.45(dd,OCHCO).
10	74	78-79 ³ [79-79.5] ⁴	1790(lactone C=O) 1700(ketone C=O)	2.55(m,4H,2XCH ₂),5.90(m,CH), 7.35-7.80(m,3H,aromatic protons), 7.85-8.10(m,2H,aromatic protons).
12	78	129-131 ^{2,3}	1784(lactone C=O) 1716(ketone C=O)	2.62(dd,CH), 3.17(dd,CH), 3.9(s,3H, OCH ₃), 4.17(m,CH), 5.03(d,OCHCO),6.90(d,aromatic C-H, 7.00(dd, aromatic CH), 7.75(d, aromatic CH).
14	68	oil ^{1,2}	1737(lactone C=O) 1723(ketone C=O)	0.90(t,3H,CH ₂ CH ₃), 1.50(m,2H,CH ₂ ,CH ₂ , CH ₃), 2.20(t,2H,CH ₂ ,CH ₂ ,CH ₃), 2.48(s,4H, 2XCH ₂), 4.50(s,1H,CH).
16	79	89-90 ^{1,2}	1737(lactone C=O) 1731(ketone C=O)	7.35-8.60(m,10H,aromatic protons), 8.90(m,aromatic CH).
18	48	oil ^{1,2}	1788(lactone C=O) 1728(ketone C=O)	2.30(s,6H,2XCOCH ₃), 2.60(m,4H,2XCH ₂).
20	36	151-153 ^{1,2,3}	1739(Lactone C=O) 1710(Ketone C=O)	2.62(m,4H,2XCH ₂), 2.90(m,4H,2XCOCH ₂), 3.90(s,3H,OCH ₃), 6.90(m,2H,aromatic protons),7.70(m,aromatic CH).

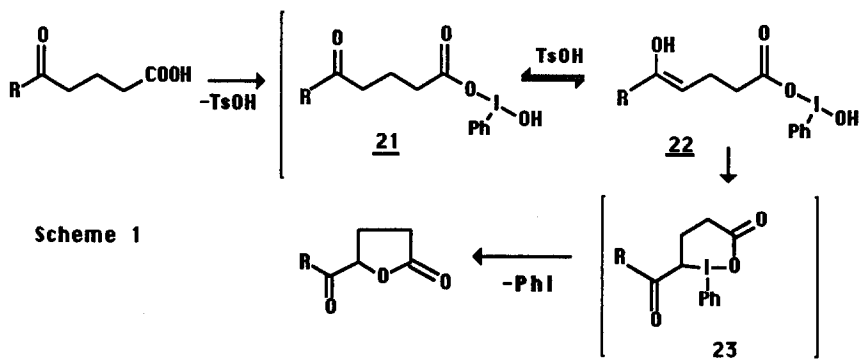
¹ Compound was purified by column chromatography using neutral alumina as the stationary phase and dichloromethane:hexane (1: 9) as eluents.

² Compound showed correct carbon and hydrogen analysis.

³ Solvent of crystallization was dichloromethane/hexane.

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A possible pathway for the intramolecular cyclization may involve (i) ligand exchange between the carboxylate function of starting material and $C_6H_5I(OH)OTs$ to give intermediate 21, (ii) intramolecular hyperiodination alpha to the keto function via the enol 22, to give the cyclic intermediate 23, (iii) formation of C-O bond may occur via ligand coupling and reductive elimination of iodobenzene (Scheme 1).



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12. 13 & 15 respectively prepared by condensing the kinetic enolate anion of 2-butanone and 2-acetyl naphthalene with succinic anhydride.
13. 17 was prepared by the hydrolysis of the corresponding methyl ester available from Aldrich.
14. 19 was prepared by condensing the enolate anion of 6-methoxy α -tetralone with succinic anhydride.

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