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A FACILE SYNTHESIS OF δ-VALEROLACTONES BY PHOTOANNELATION[1]

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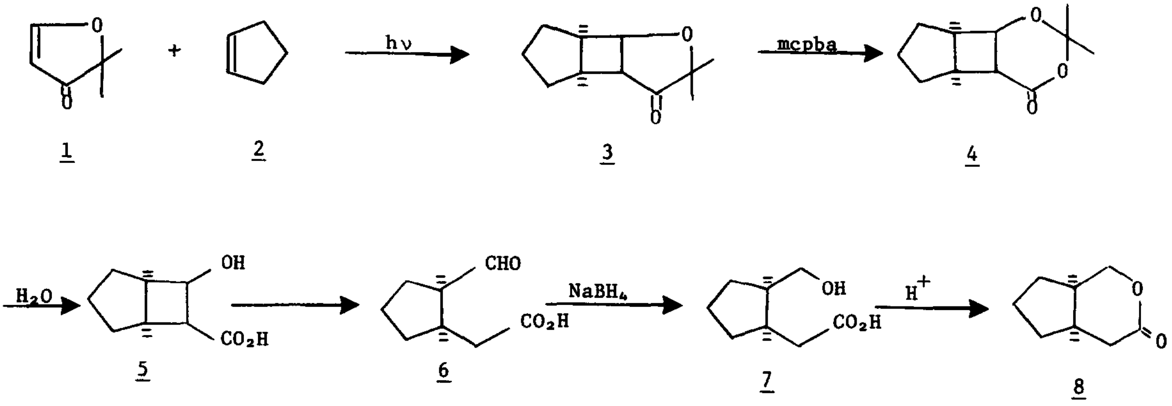
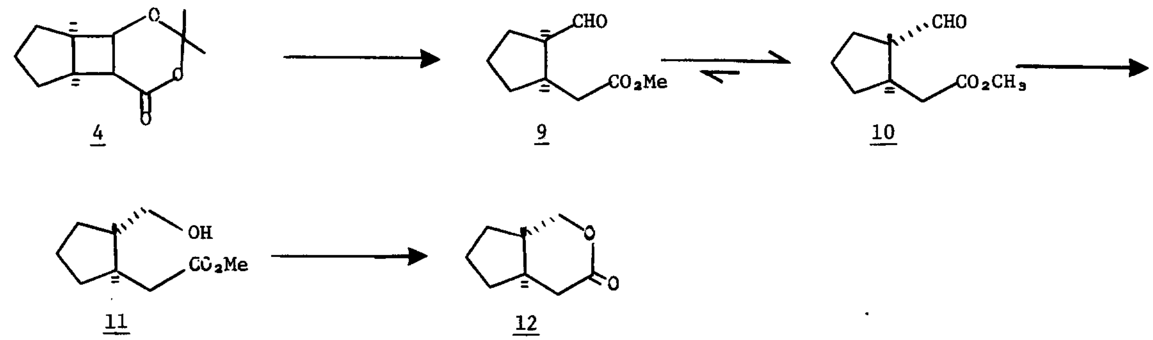
In conjunction with our studies of the photochemical annelation of alkenes with α-formyl ketones[2] and their equivalents, we have been utilizing 5,5-dimethyl-4-oxacyclopentenone (1) as an α,β-unsaturated carbonyl photopartner.[3] It has been shown that the cyclobutane photoproducts from 1 and alkenes can be readily elaborated to cyclohexenones by one of two alternative procedures.[4]

Recently it occurred to us that these same products are ideally suited for conversion to δ-lactones, and because of the high level of interest in such lactones and their α-methylene counterparts,[5-7] we have evolved the following reaction sequences for their formation. The conversion of photoproduct 3 to lactone 8 is illustrative. Baeyer-Villiger oxidation of 3 with *m*-chloroperbenzoic acid yielded oxalactone 4, which then afforded hydroxyacid 5 on exposure to aqueous methanol.[8] Treatment of 5 with NaBH$_4$ in refluxing isopropanol followed by an acidic workup then produced the *cis* fused δ-lactone 8 in 78% yield (70% overall yield from cyclopentene).

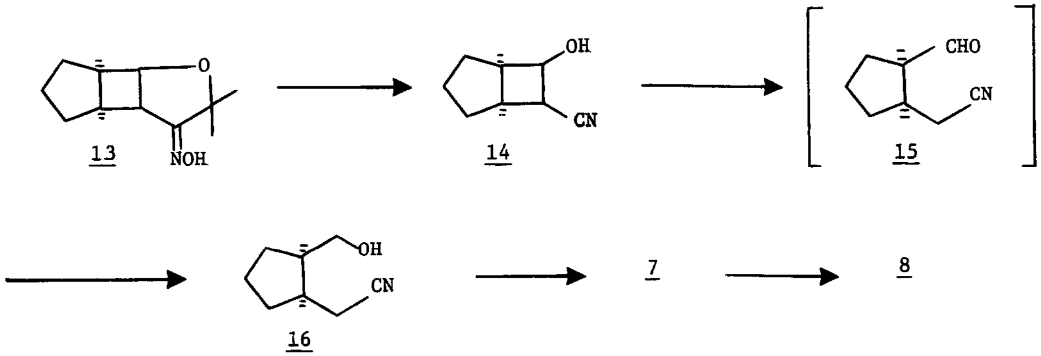


Alternatively retroaldol cyclobutane opening to the corresponding methyl ester 9 (methanol/H$_3$O$^+$/Δ) followed by NaBH$_4$ reduction and acidic workup afforded the *trans* fused lactone 12 due to the rapid equilibration of 9 to the more stable *trans* isomer. Thus those photoproducts which have a hydrogen on the cycloalkene carbon adjacent to the latent aldehyde can be converted to either *cis* or *trans* fused δ-lactones, depending on reaction conditions.



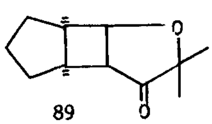
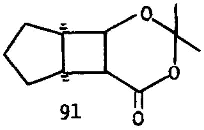
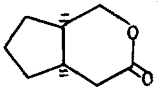
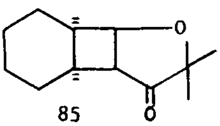
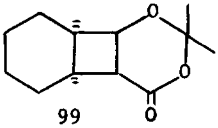
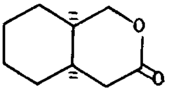
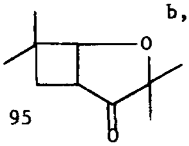
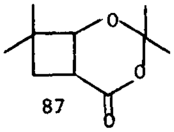
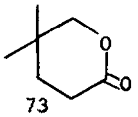
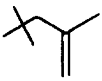
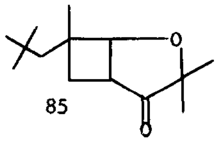
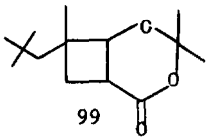
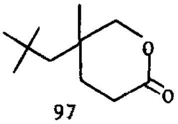
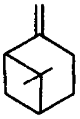
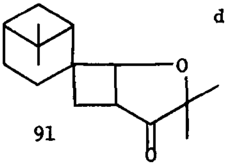
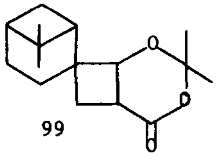
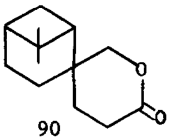
A related method for the conversion of 3 to cis lactone 8 involved the formation of hydroxy nitrile 14 via Beckmann fragmentation[9] of oxime 13. Treatment of 14 with $NaBH_4$ as before followed by base hydrolysis then yielded 8 in good yield. In some instances photoproducts have proved to be resistant to Baeyer-Villiger oxidation under a variety of conditions[4], and thus the Beckmann fragmentation route provides a useful alternate pathway for the formation of δ-lactones. In our hands, however, the production of lactones from the Baeyer-Villiger sequence was preferable in most cases, and the results of several typical experiments are collected in the Table.[12]

In summary we have presented a highly efficient method for the formation of δ-lactones which should prove general value in future synthetic efforts. A representative experimental procedure for the conversion of 3 to 8 follows.



Cis δ-Lactone (8): To a solution of 4.17 g (23.2 mmole) of pure photoproduct 3 in 200 ml dry CH_2Cl_2 was added 6.70 g (33.1 mmole) m-chloroperbenzoic acid (85%) and 5.20 g (53.1 mmole) $NaHCO_3$ and the mixture was stirred at room temperature for 5 hrs. The reaction was quenched with 10% Na_2SO_3 (25 ml) and after stirring for 10 minutes the layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 x 25 ml). The combined organic layers were washed with saturated $NaHCO_3$, dried (Na_2SO_4), and concentrated to afford 4.12 g (91%) of a clear oil, homogeneous by tlc. NMR (CCl_4) δ 1.52 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 1.50-2.06 (m, 6H, $(CH_2)_3$), 2.45-2.82 (m, 2H, cyclobutane H's), 2.93-3.16 (m, 1H, $CHCO_2C(CH_3)_2$), 4.19 (dd, J=2Hz & 6Hz, 1H, $CHOC(CH_3)_2$); ir (film) 1735, 1376, 1295, and 1257cm^{-1}.

Table: Formation of δ-Lactones by Photoannelation[a]

Alkene	Photoproduct %	Oxalactone %	δ-Lactone %	Overall %
	 89 [b]	 91	 86	70
	 85	 99	 92 [c]	77
	 95 [b,d]	 87	 73 [e]	60 [f]
	 85 [d]	 99	 97	82
	 91 [d]	 99	 90 [g]	81

[a] Yields have not been optimized; all new photoproducts and δ-lactones gave satisfactory (±0.3%) elemental analyses and consistent spectral data. [b] Reference 3. [c] Reference 10. [d] All 1,1-disubstituted ethylenes studied to date give a single photoproduct regiochemistry, with a mixture of stereoisomers where possible. [e] Reference 11. [f] The low yield associated with this particular lactone is most likely the result of its greater volatility relative to the other lactones studied. [g] A 5:1 mixture of stereoisomers, the major one presumably resulting from initial photoaddition to the least hindered side of β-pinene.

A solution of 547 mg (2.75 mmole) of this crude oxalactone in 50 ml CH_3OH and 2 ml H_2O was heated at reflux for 1.5 hours whereupon it was cooled and concentrated yielding 433 mg (100%) of a very viscous clear oil, hydroxy acid *5*. NMR (acetone d_6) δ 4.11 (dd, J=4Hz & 8Hz, 1H, $C\underline{H}OH$). Without purification this material was dissolved in 50 ml 2-propanol to which 789 mg (20.9 mmole) $NaBH_4$ was added, and the resulting mixture heated at reflux for 6 hr. After cooling to room temperature the reaction was cautiously quenched with 10% HCl (10 ml) whereupon the mixture was extracted with CH_2Cl_2 (3 x 50 ml). The combined organic extracts were washed with saturated $NaHCO_3$ (2 x 15 ml), dried (Na_2SO_4), and concentrated to yield 334 mg (80%) of a clear oil homogeneous by glc and tlc. Evaporative distillation (100°, 0.1 mm Hg) afforded the analytical sample of *cis* lactone *8*. NMR (CCl_4) δ 1.21-2.09 (M, 6H, $(C\underline{H}_2)_3$), 2.24-2.66 (M, 4H, CH_2CO & $C\underline{H}$), 4.04 (AB of ABX, $\Delta\nu^{AB}$=28Hz, J_{AB}=10Hz, J_{AX}=3.5Hz, J_{BX}=6Hz, 2H, $C\underline{H}_2O$); ir (film) 1725, 1245, 1158, and 1257cm^{-1}.

Anal. calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63.
Found: C, 68.30; H, 8.84.

References and Notes

1. Financial assistance from a Biomedical Sciences Support Grant, administered by Duke University, is acknowledged with appreciation.
2. (a) S. W. Baldwin, R. E. Gawley, R. J. Doll, and K. H. Leung, *J. Org. Chem.*, *40*, 1865 (1975); (b) S. W. Baldwin and R. E. Gawley, *Tetrahedron Lett.*, 3969 (1975).
3. Previous use of (*1*) as a photochemical addend has been reported. (a) P. Margaretha, *Chimia*, *29*, 203 (1975); (b) P. Margaretha, *Tetrahedron*, *29*, 1317 (1973); (c) P. Margaretha, *ibid.*, *27*, 6209 (1971); (d) P. Margaretha, *Tetrahedron Lett.*, 4891 (1971).
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7. Several methods exist for the conversion of γ- and δ-lactones to their α-methylene counterparts. See, for example, P. A. Grieco and K. Hiroi, *J. Chem. Soc., Chem. Commun.*, 1317 (1972).
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11. G. Descotes, J.-C. Martin, and G. Labrit, *Bull. Soc., Chim. Fr.*, 4151 (1969).
12. For a synthesis of δ-lactones which is comparable in scope see C. G. Chavdarian and C. H. Heathcock, *J. Org. Chem.*, *40*, 2970 (1975).

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