Conversion of 5-Oxoalkanals to δ-Lactones by an Intramolecular Tishchenko Reaction

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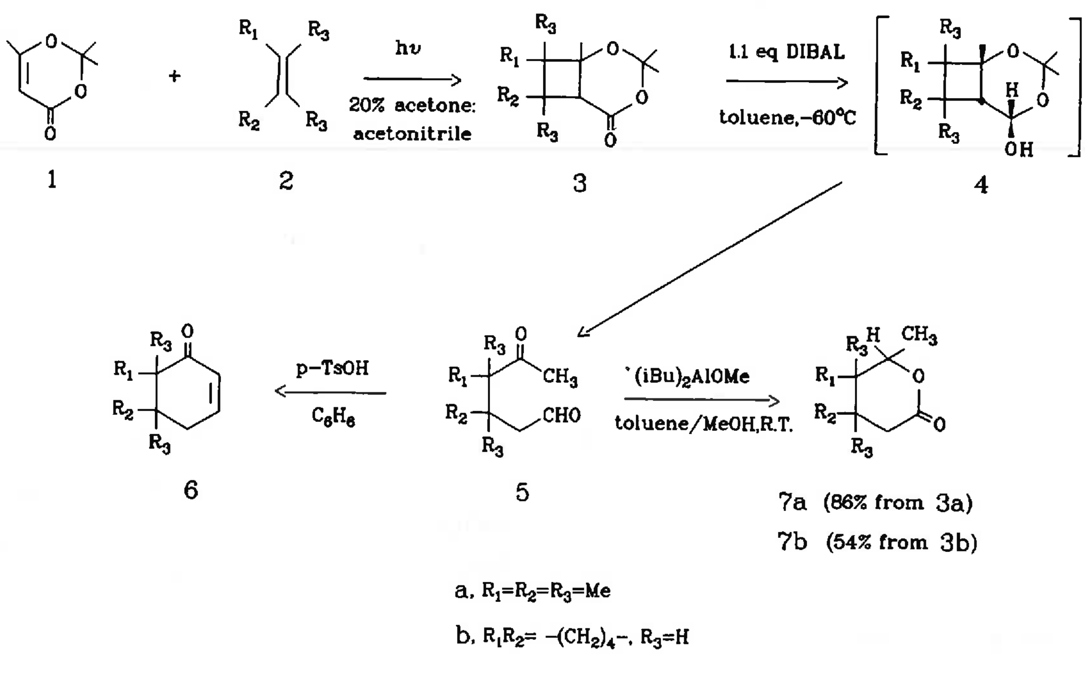
Abstract: Diisobutylaluminum hydride reduction of photoadducts **3** (7,8-tri- and tetrasubstituted 1,3,3-trimethyl-2,4-dioxabicyclo-[4.2.0]octan-5-ones), derived from 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**1**), gave δ-lactones **7** in good to excellent yields if the workup involved a methanol quench followed by removal of the solvent. We propose that the reaction proceeds by an intramolecular Tishchenko reaction of the intermediate 5-oxoalkanal **5** and is catalyzed by the Lewis acid diisobutylaluminum methoxide, **8**. A deuterium labelling experiment supports the mechanistic proposal and the conversion of 5-oxoalkanals other than **5** illustrates the scope of the procedure. To our knowledge, this is the first report of a true intramolecular Tishchenko reaction.

Photochemical cycloadditions of dioxolenones such as 1 with alkenes 2 have been shown by Baldwin[1] to yield adducts 3, which upon reduction with diisobutylaluminum hydride (DIBAL) give 5-oxoalkanal 5 via the hemiacetal 4 (Scheme 1). Aldol cyclization of 5 using p-toluenesulfonic acid in benzene gives substituted cyclohexenones 6 in good yield. We have found that by a simple variation in the workup procedure for the reaction, it is possible to completely change the nature of the products obtained. This letter outlines the modified procedure that effects this change, the structures of the new products and a proposed mechanism for their formation.

Adducts 3a or 3b[1] were reduced with DIBAL as described in the procedure below. The reduction reaction was then quenched with excess methanol and the mixture was allowed to warm from -60°C to room temperature. But at this point, rather than treating the mixture with dilute acid as was done previously,[1] the methanol-toluene solvent mixture was simply removed in vacuo and to our surprise the lactone products 7a or 7b (3:1 epimeric mixture[2]) were obtained in good to excellent yields. For product yields see Scheme 1 and for experimental details see the procedure below.

A number of additional experiments were conducted to provide mechanistic information regarding the formation of the lactone products. For this purpose, pure 5a was prepared from 3a in 90% yield using the standard acidic workup after the reduction.[1] We were interested in observing the behaviour of 5a under basic or Lewis acid conditions in case either of these conditions was present in our modified workup procedure.

Treatment of 5a with 1.1 equivalents of $NaOCH_3$ in toluene-MeOH (-60° to r.t.) gave the aldol condensation product 6a in 61% yield. Thus 7a could not have been formed by a base-catalyzed Cannizzaro-type reaction followed by lactonization. However, when 5a was treated with 1.1 equivalents of diisobutylaluminum methoxide, 8 (prepared by addition of excess methanol to DIBAL at -60°C) in toluene (-60°C to r.t.) and the solvents removed in vacuo, lactone 7a was isolated in 85% yield.

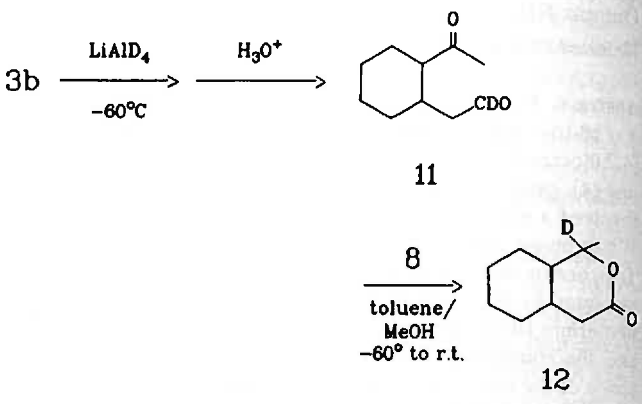


Scheme 1

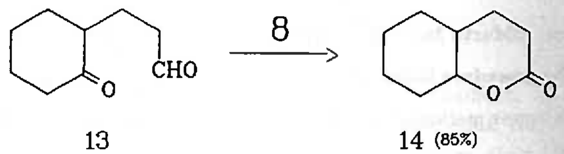
Neither aluminum methoxide, $Al(OMe)_3$, nor aluminum ethoxide, $Al(OEt)_3$, effected the conversion of **5a** to **7a**.

We propose that lactone **7a** is formed by an intramolecular mixed Tishchenko reaction. This reaction normally involves conversion of two moles of an aldehyde to an ester in the presence of an aluminum alkoxide,[3,4] although mixed Tishchenko reactions involving an aldehyde and a ketone have been reported.[4,5] The intramolecular mechanism proposed in Scheme 2 for the conversion of **5a** to **7a** is similar to one proposed by Lin[4,5] for the intermolecular conversion of aldehydes to esters in the presence of aluminum isopropoxide. We suggest that the Lewis acid catalyst **8**, which is highly oxygenophilic,[6] coordinates with the aldehyde oxygen in **5a** to form **9**. The nucleophilic ketone oxygen then attacks the carbocationic centre in **9** to yield **10**, which after hydride transfer and loss of the catalyst gives lactone **7a**.[7] Of course, in the overall conversion of adduct **3a** to **7a**, the requisite **5a** is formed from the reduction product **4a** by spontaneous loss of acetone followed by fragmentation and the catalyst **8** is formed by alkoxide exchange when the reaction mixture is quenched with methanol. To our knowledge, this is the first report of a true intramolecular Tishchenko reaction although there have been two reports of bimolecular reactions to form complexes which then underwent an intramolecular hydride transfer in a Tishchenko-like reduction.[8,9]

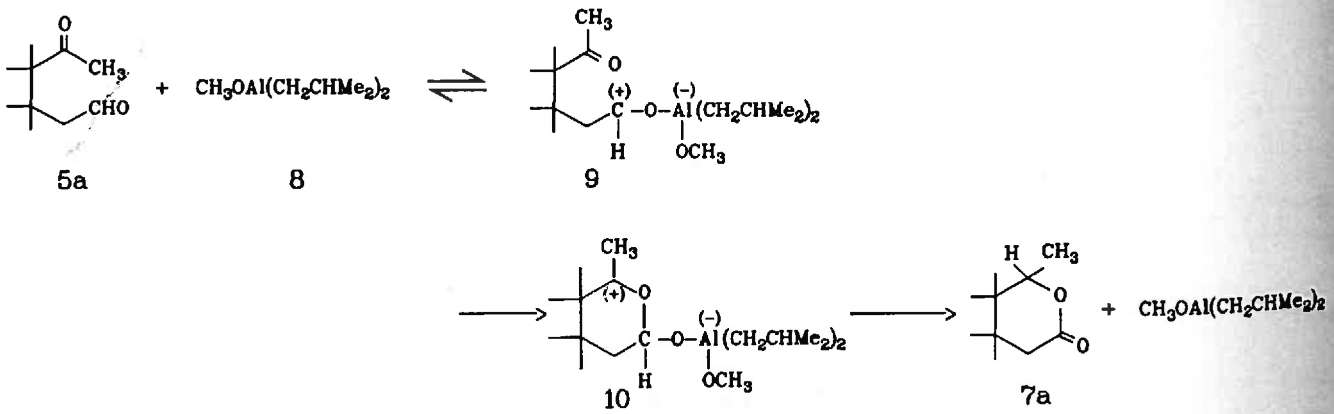
A deuterium isotope experiment provided further evidence for this proposed mechanism. Reduction of adduct **3b** with $LiAlD_4$ at -60° followed by quenching with dilute acid gave the deuterated aldehyde **11** as a mixture of epimers, which upon treatment with catalyst **8** gave deuterated lactone **12**. The ^1H NMR, IR and mass spectra of **12** were entirely consistent with the structure proposed, particularly the location of the deuterium atom. This experiment clearly establishes that the aldehyde hydrogen is the source of the hydride required for the reduction of the carbonyl group.[10]



To explore briefly the scope of this Tishchenko reaction, we prepared a structurally different 5-oxoalkanal using an enamine precursor rather than a dioxolenone adduct. Substrate **13** was prepared from the morpholine enamine of cyclohexanone and acrolein.[11] Treatment of **13** with catalyst **8** using our standard conditions gave in 85% yield octahydrocoumarin **14** as an 85:15 trans/cis mixture.[12] Thus, the conversion of 5-oxoalkanals to δ-lactones proceeds whether the ketone function is in the side chain or is part of a ring. Attempts to convert 2-oxocyclohexane-acetaldehyde to a γ-lactone were unsuccessful and suggest that our procedure is restricted to the preparation of δ-lactones.



We plan to investigate further the scope of this methodology for the conversion of dioxolenone photoadducts and 5-oxoalkanals to δ-lactones and to determine the importance of the



Scheme 2 **Mechanism for Conversion of 5a to 7a**

size and nature of the substituents on the aluminum catalyst.[13-15] Preliminary results reported here suggest that the choice of substituents attached to aluminum (e.g. **8**) is critical to the success of the transformation.

Procedure: To a stirred solution of adduct **3a** (100mg, 0.44mmol) in 5 mL of dry toluene at -60°C was added 1.5M DIBAL in toluene (0.32mL, 0.48mmol). The reaction was stirred at -60°C for 1.0h, 5 mL of anhydrous methanol was added dropwise, and the solution was allowed to warm to room temperature.[16] The toluene-methanol solvent mixture was removed in vacuo (bath temperature 30°C), the residue was partitioned between water and ether and the aqueous phase was extracted with ether (2X). The combined ether phases were washed with water and with brine and then dried (anhydrous $MgSO_4$). The solvent was removed and the residue was purified by MPLC (20% EtOAc-hexanes) to give 64 mg (0.38mmol, 86%) of lactone **7a**, m.p. 105-106°C.

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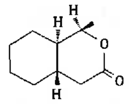
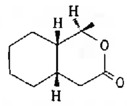
References and Notes

(1) Baldwin, S.W.; Wilkinson, J.M. J. Am. Chem. Soc. 1980, 102, 3634.

(2) A 3:1 trans/cis mixture of **5b** yielded a 3:1 mixture of **7b(i)** and **7b(ii)**. The ^1H and ^{13}C NMR spectra of this mixture showed excellent agreement with the data reported for the pure compounds: Fujiwara, Y.; Okamoto, M. Chem. Pharm. Bull. 1989, 37, 1458.


7b(i)


7b(ii)

(3) Ogata, Y.; Kawasaki, A.; Kishi, I. Tetrahedron 1967, 23, 825.

(4) Ogata, Y.; Kawasaki, A. Tetrahedron 1969, 25, 929.

(5) Lin, I.; Day, A.R. J. Am. Chem. Soc. 1952, 74, 5133.

(6) Maruoka, K.; Yamamoto, H. Angew. Chem. Int. Ed. Eng. 1985, 24, 668.

(7) As a 3:1 trans/cis mixture of **5b** yields a corresponding 3:1 mixture of **7b** isomers,[2] this hydride transfer step is highly stereoselective for each of these epimers.

(8) Burkhardt, E.R.; Bergman, R.G.; Heathcock, C.H. Organometallics 1990, 9, 30.

(9) Evans, D.A.; Hoveyda, A.H. J. Am. Chem. Soc. 1990, 112, 6447.

(10) A referee had suggested that an isobutyl group in catalyst **8** might be the source of hydride.

(11) Allan, R.D.; Cordiner, B.G.; Wells, R.J. Tetrahedron Lett. 1968, 6055.

(12) ^1H and ^{13}C NMR spectra of the mixture were compared with the data reported for the pure isomers: Griffiths, D.V.; Wilcox, G. J. Chem. Soc., Perkin Trans. II 1988, 431.

(13) $(C_2H_5)_2AlOC_2H_5$ has been employed in the intramolecular aldol condensation of hindered diketones[14] and the properties and reactions of bulky alkylaluminum bisphenoxides have been reported.[15]

(14) ApSimon, J.W.; Lawuyi, R.F. Syn. Commun. 1987, 17, 1773.

(15) (a) Maruoka, K.; Nagahara, S.; Yamamoto, H. Tetrahedron Lett. 1990, 31, 5475. (b) Power, M.B.; Barron, A.R. Polyhedron 1990, 9, 233.

(16) At this point, if the reaction mixture was stirred for 48h., then worked up under acidic conditions, **5a** and **7a** were formed in a ratio of 1:2.