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A VERSATILE TITANIUM-MEDIATED PROCEDURE FOR DIVERSIFIED BISFUNCTIONALIZATION OF γ-LACTOLS

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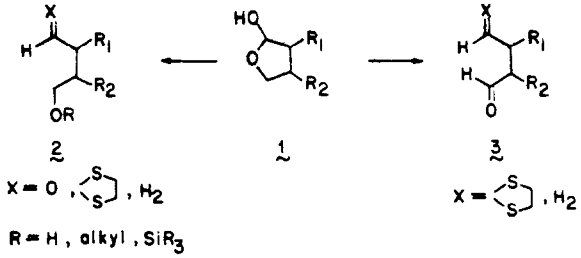
Summary: Reported here is a procedure whereby γ-lactols may be trapped in masked hydroxy aldehyde form suitable for chemical manipulation of either terminus.

The role of γ-lactones as useful intermediates for the elaboration of complex organic structures would be augmented by the availability of a mild cleavage procedure which could lead to control of functionality at either oxygenated carbon. Although γ-lactols (1) are efficiently produced by diisobutylaluminum hydride reduction of such substrates, they are frequently recalcitrant to ring opening,[2-4] in contrast to the behavior of larger lactols.[5,6] The already strong propensity of 1 to exist and react in the cyclic hemiacetal form is normally intensified by ring substitution and annulation. The need for effecting conversions of the type 1 → 2 and 1 → 3 in connection with several synthetic programs in these laboratories has prompted the development of an efficient and generally applicable protocol.



The methodology takes advantage of the stronger nucleophilicity of sulfur compared to oxygen to capture the masked aldehyde as the ring-opened ethylene thioacetal. Although a similar reaction has been observed for a six-membered ring hemiacetal using boron trifluoride etherate catalysis,[5c] it was anticipated that more forcing conditions should be required in order to cleave the endocyclic carbon-oxygen bond of γ-lactols. We envisioned that Lewis acids based upon aluminum[7] and titanium,[8] reagents capable of forming covalent bonds with oxygen, would best suit our purposes.[9] In particular, titanium tetrachloride, which does not form covalent bonds readily with thiols, but rather generates octahedral complexes,[10] seemed especially promising.

To evaluate the validity of this hypothesis, 4 was reacted with ethanedithiol in dichloromethane in the presence of a variety of catalysts (Table I). In each case, the initial formation of 5 was rapid. Expectedly, $BF_3 \cdot Et_2O$ and the protic acid reagents cleanly gave only 5. $AlCl_3$ and $AlMe_3$ generated unfavorable amounts of the desired product 6, irrespective of reaction time or quantity of Lewis acid. On the other hand, $TiCl_4$ allowed rapid and exclusive formation of 6 in excellent yield. Furthermore, complete reaction was attained even at -78°C. Thus, this reagent apparently provides a degree of selective coordination within 5 adequately high to foster enhanced sulfur nucleophilicity.

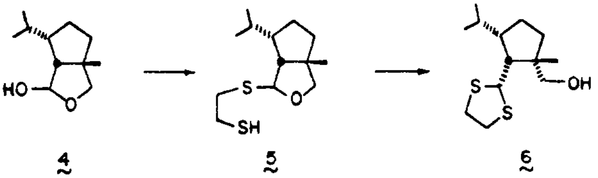
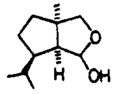
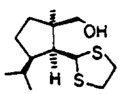
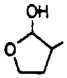
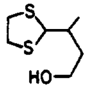
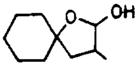
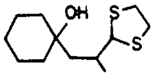
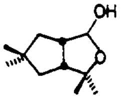
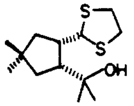
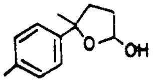
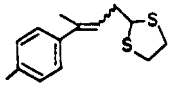
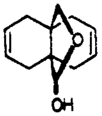
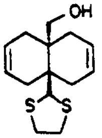
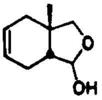
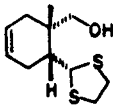


Table I. Acid-Catalyzed Reactions of 5 with 1,2-Ethanedithiol.

Catalyst	Ratio 5:6 (%)	Combined yield (%)
Py•HOTs	100:0	> 95
TsOH	100:0	> 95
$BF_3 \cdot Et_2O$	100:0	92
$AlCl_3$	90:10	94
$AlMe_3$	90:10	90
$TiCl_4$	0:100	85

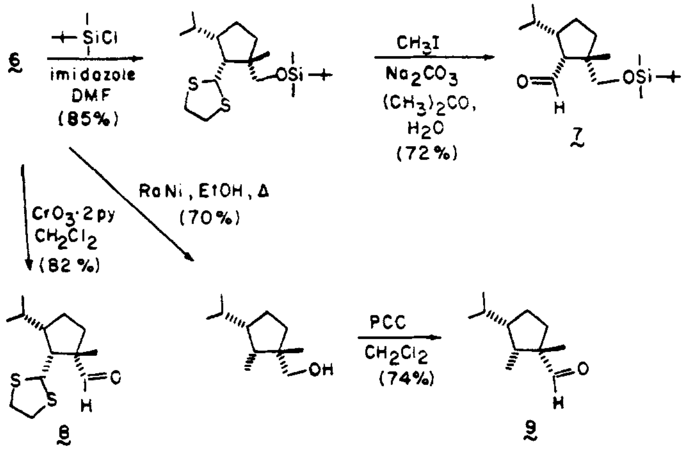
Comparably advantageous results were seen when a variety of γ-lactols were submitted to the established reactions conditions (Table II). Efficiency does not appear to be linked to the substitution pattern present in the substrate. While a simple tertiary alcohol is stable to the reaction conditions (Case 4) and can be isolated in high yield, the added benzylic character present in Case 5 leads to eventual dehydration. Although the oxathioacetals isolated from the other experiments are shelf stable, they smoothly undergo analogous $TiCl_4$-promoted

Table II. $TiCl_4$-Promoted Ring Opening of γ-Lactols with 1,2-Ethanedithiol.

Example no.	γ-Lactol	Product	Yield (%)
1			85
2			72
3			83
4			86
5			70
6			70
7			75

conversion into the corresponding thioacetals. Their role as intermediates is thereby given added credence.

The ring cleavage process may also be achieved by using 1,3-propanedithiol under somewhat more rigorous conditions, thus providing the umpolung of lactone reactivity. Other usefully functionalized synthetic intermediates may also be derived, the conversion of **6** into **7**-**9** being exemplary. The readiness with which aldehyde functionality may be introduced at either side-chain position (compare **7** versus **8** and **9**) is particularly notable. From the practical viewpoint, the lactols need not be purified prior to use. In addition, all thioacetal products may be stored in the pure state at room temperature; no example of reversion to the cyclic oxathioacetal form has been observed.



The methodology outlined above clearly fulfills the role of a versatile and efficient tool for the position-selective bis-functionalization of lactols which is expected to have wide applicability. The flexibility, mild nature, and possible tolerance to varied functional groups should now remove most, if not all, impediments to exploitation of this strategem in the elaboration of complex targets.[11]

References and Notes

(1) (a) NATO Postdoctoral Fellow of the Science and Engineering Research Council, 1981-1983. (b) Continental Oil Company Fellow, 1982-1983.

(2) For recent examples, see: Schmidt, R. R.; Abele, W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 302; Caruso, A. J.; Polonsky, J.; Rodriguez, B. S. *Tetrahedron Lett.* **1982**, 2567.

(3) Exceptions are known when intramolecular rearrangement pathways can take place; see Takano, S.; Yonaga, M.; Chiba, K.; Ogasawara, K. *Tetrahedron Lett.* **1980**, 3697.

(4) Phosphorus ylides are well known to be able to capture γ-lactols as their acyclic hydroxy aldehyde tautomers in variable yield; chain extension of the more oxidized carbon results [Bindra, J. S.; Bindra, R. "Prostaglandin Synthesis," Academic Press, Inc. 1977; Boland, W.; Jakoby, K.; Jaenicke, L. *Helv. Chim. Acta* **1982**, *65*, 2355; Corey, E. J.; Shimoji, K. *J. Am. Chem. Soc.* **1983**, *105*, 1662].

(5) Consult, for example: (a) Crandall, J. K.; Huntington, R. D.; Brunner, G. L. *J. Org. Chem.* **1972**, *37*, 2911. (b) Nicolaou, K. K.; Magolda, R. L. *Ibid.* **1981**, *46*, 1506. (c) Roush, W. R.; D'Ambra, T. E. *Ibid.* **1980**, *45*, 3927.

(6) Direct reaction of δ-lactones with bis-(dimethylaluminum)-1,3-propanedithiolate leads to cleavage but maintains the carbonyl group at the carboxyl oxidation level [Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 5829; Chamberlin, A. R.; Chung, J. Y. L. *Tetrahedron Lett.* **1982**, 2619]. Relevantly, the products formed from γ-lactones appear exceedingly prone to recyclization.

(7) Ong, B. S. *Tetrahedron Lett.* **1980**, 4225.

(8) Dumar, V.; Dev, S. *Tetrahedron Lett.* **1983**, 1289.

(9) Recently, it has been shown [Corey, E. J.; Shimoji, K. *Tetrahedron Lett.* **1983**, 169] that magnesium and zinc triflates catalyze the efficient thioketalization of ketones.

(10) (a) Bradley, D. C.; Hammersley, P. A. *J. Chem. Soc. (A)* **1967**, 1894. (b) Chatterjee, S.; Sukharni, D.; Gupta, V. D.; Mehrotra, R. C. *Ind. J. Chem.* **1970**, *8*, 362.

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