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DIRECT BUTYROLACTONE PRODUCTION USING TIN HYDRIDE

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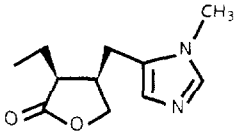
Abstract: Use of $HSnBu_3$ for the reductive cyclization of suitable alpha-bromo allylic esters affords 2,3-disubstituted butyrolactones.

The butyrolactone functionality appears in numerous natural products such as pilocarpine 1 (1) and deoxypodorhizon 2 (2). Biological activity found in many of these compounds has prompted considerable synthetic effort (3).



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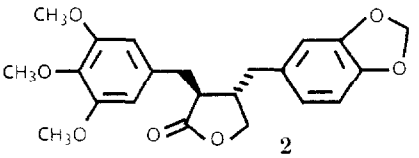

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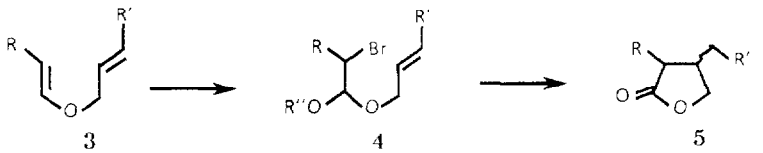
Typical published examples of straightforward sequences to 2,3-disubstituted butyrolactones include Michael addition/enolate alkylation (4) and dianion coupling/selective hydrolysis (5) methodologies. An alternative route to such targets involves a convergent strategy that employs the template effect provided by a suitably functionalized starting material in which an ether oxygen links the two halves of the precursor molecule. This approach was pioneered by Stork (6) and by Ueno (7) in their development of bromoacetal cyclization chemistry (i.e. 3 to 4 to 5). Unfortunately, syntheses of complex examples of 3 are quite challenging and several steps are required to go from 4 to 5. Therefore, we have investigated a modified free radical template sequence, employing a bromoester in place of the bromoacetal.

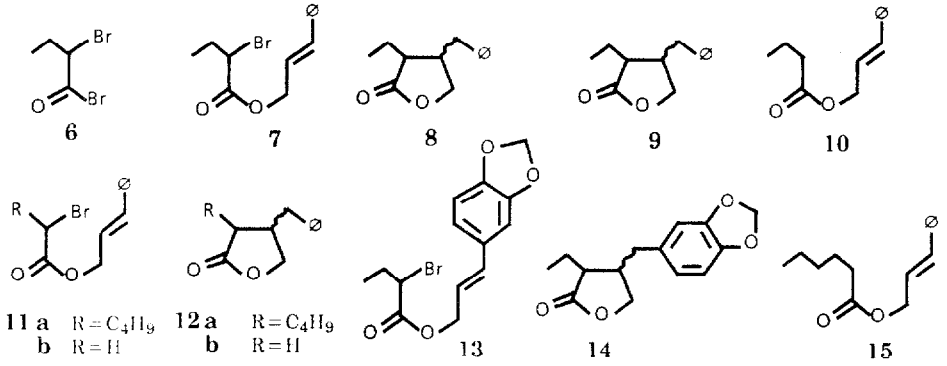


3 4 5

Many potential substrates for a radical chain-based cyclo-dehalogenation route to butyrolactones are easily accessible due to the existence of efficient procedures for preparing esters (8), for alpha-halogenating carboxylic acid dianions (9), and for generating allyl alcohol derivatives (10). Although the literature suggests (11) that haloester allyl ether

cyclo-dehalogenations are often sluggish, we now report that, for many of the substrates depicted below, this cyclization proceeds efficiently.

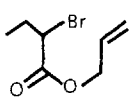
As a model for targets of the pilocarpine type, we transformed (12) commercially available acid halide 6 into ester 7 (chromatographed yield = 77%). Slow addition of a $HSnBu_3$ solution containing 15 mole % of AIBN to a refluxing solution of 7 in dry benzene followed by heating at reflux for 10 hours, led to the desired lactone 8 (chromatographed yield = 50% (12)), presumably via formation of the intermediate benzylic radical 9. A recovered non-polar fraction proved to be the dehalogenated ester 10, which was isolated in ca. 35% yield. Similar experiments performed with the analogous bromoesters 11a and 13 gave smooth conversion to the desired lactones 12a and 14 (13) (chromatographed yields of 42.5% and 39%, respectively). A preliminary experiment using bromoester 11b gave only a small amount of lactone 12b (chromatographed yield = 19.6%) (14).



Isolation of the products from a $HSnBu_3$ reaction often (15) involves removal of benzene from the cooled reaction mixture, dilution with acetonitrile and ligroin, separation of the resulting immiscible layers, and removal of the volatiles from the acetonitrile layer. Alternatively, evaporation of (15) of the crude benzene reaction mixture to a syrup and direct column chromatography generally afforded a better recovery of the lactonic fraction.

Using substrate 11a, we tried to discern any effect caused by the rate of addition of the $HSnBu_3$/AIBN solution to the refluxing bromoester. Initial rapid mixing of 11a, $HSnBu_3$, and AIBN followed by prolonged heating of the resulting benzene solution gave only a low yield of butyrolactone. Addition of $HSnBu_3$/AIBN over 1.5 hrs. produced 37% of lactone 12a and 45% of ester 15 (which contained, by proton NMR, 2-3 % of 11a). When the addition was extended over 3.8 hrs., we isolated 42.5% of analytically pure lactone 12a. A 5 hour rate of addition afforded 39.5% of 12a and only 32% of 15. TLC of the crude reaction mixture also indicated the presence of polar by-products.

The allylic esters 16, 17, and 18 (readily available by esterification of acid chloride 6 with allyl, crotyl, and dimethylallyl alcohols, respectively) gave crude reaction mixtures exhibiting a butyrolactone carbonyl IR stretch. The butyrolactone corresponding to 18 (16) was obtained analytically pure in a chromatographed yield of 33.6%.



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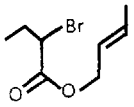

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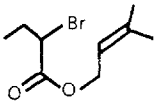

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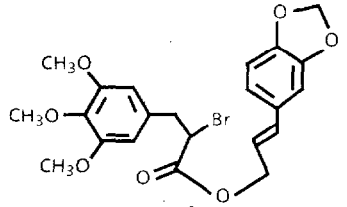
As a model for unsymmetrical lignans, we attempted the cyclization of bromoester 19. Preparation of this substrate involved reduction (10) of methyl ester 20 (-17°C; 1.4 eq. $LiAlH_4$; THF; 1 hr.; recryst. from CCl_4; mp 72-73°C) as well as bromination (9) of the dianion derived from 21 (-20°C -RT; 2 eq LDA; excess CBr_4; recryst. from CCl_4; mp 84-85°C). After the bromoacid was converted into the acid chloride ($(COCl)_2$; heat at 50°C in benzene), esterification (THF; RT; 2 eq. pyridine) followed by chromatography gave pure 19. Cyclization via slow addition of $HSnBu_3$/AIBN in benzene to a refluxing solution of 19 in benzene provided the desired (5a) butyrolactone 2 (diastereoisomeric mixture = ca. 4:1 trans:cis (by comparison with authentic material) (chromatographed yield = 40%)).



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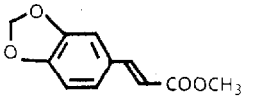

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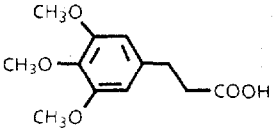

21

Investigations are now underway to optimize and to extend this cyclization approach.

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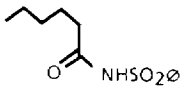
12.) All new compounds exhibited satisfactory analytical properties. Cyclization yields are not optimized but are reproducible.
13.) In order to prepare an authentic sample of butyrolactone **12a** for comparison, we employed a dianion coupling/reductive hydrolysis sequence (5) beginning with acylsulfonamide **22** (converted to its corresponding dianion) which was added via cannula transfer to a -78°C solution of the sodium salt (generated by reaction with 1 eq. of NaH in THF at -20°C) of iodocarboxylic acid **23**. After warming to RT, the reaction mixture was worked-up and the acid/acylsulfonamide **24** was partially purified by flash chromatography. Selective reduction with BH_3-THF (-30°C in 4:1 Et_2O:THF), hydrolysis (1N HCl at reflux for 16 hrs.), isolation, and careful chromatography gave lactone **12a** in ca. 20% overall yield from **22**. Preliminary work involving equilibration experiments coupled with examination of the ^{13}C NMR for $HSnBu_3$-derived samples of **2**, **8**, **12a**, and **14** suggests a similar diastereoisomeric ratio of ca. 4:1 trans:cis for all four cyclizations.



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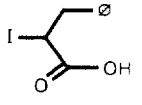

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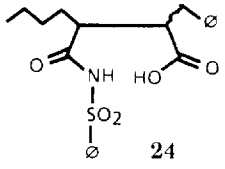

24

14.) We also isolated ca. 30% of the corresponding dehalogenated ester plus 30% of recovered **11b**.
15.) For a comprehensive review of the use of tin hydride in organic synthesis, see: Neumann, W. P. *Synthesis* 1987, 665. For a review on lactone synthesis by electron transfer and radical chemistry, see: Surzur, J.-M.; Bertrand, M. P. *Pure & Appl. Chem.* **1988**, *60*, 1659. For a general review on radical reactions in organic synthesis, see: M. Ramaiah *Tetrahedron* **1987**, *43*, 3541.
16.) The volatility of the butyrolactones corresponding to substrates **16** and **17** make isolation and accurate estimates of their yield difficult. Qualitatively, the cyclization of **18** appeared more facile than **16** or **17**.

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