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SYNTHESIS OF OXOCENONES FROM δ-LACTONES AND THEIR CONVERSION TO TRANSPOSED OXOCENES BY A REDUCTIVE FERRIER REACTION

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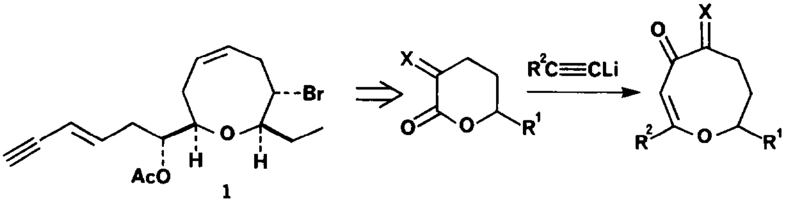
Abstract The ring expansion of δ-lactones into oxocenones by the insertion of an acetylene is reported. A reductive Ferrier reaction can be employed to convert these products into transposed oxocenes.

The oxocene laurencin[2,3], **1**, is representative of a structurally intriguing class of non-isoprenoid marine natural products.[4] Efforts to synthesize members of this class must address the problem of stereochemically controlled oxocene formation. We now report a method for the conversion of δ-lactones into oxocenones and a subsequent functionalization procedure which provides access to the 2,8-disubstituted oxocene ring system.



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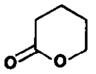
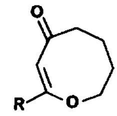
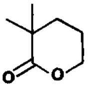
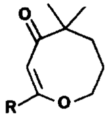
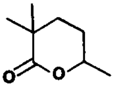
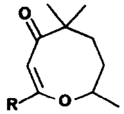
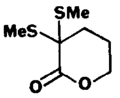
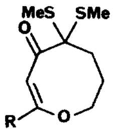
The low temperature addition of an alkynyl lithium reagent to a lactone has been studied in detail by Chabala and Vincent at Merck[5] and shown to provide the acetylenic ketone in high yield. Subsequent to that report, numerous examples have appeared which further demonstrate the synthetic utility of this reaction process.[6] We have examined this reaction with several lactones and now report that in certain cases the addition product can be induced to undergo a ring enlargement to an oxocenone when warmed to room temperature in the presence of HMPA.[7] The ring expansion is presumed to occur by ring opening of the hemiketal addition product followed by an intramolecular endocyclic conjugate addition to the resultant acetylenic ketone. The degree of success of this reaction appears to be dependent on both the nature of the alkynyl lithium reagent and the substitution pattern of the δ-lactone as the results in Table 1 suggest.

Table 1 Formation of Oxocenone from δ-Lactone

Entry	δ-Lactone	Product (yield)^{a,b}	
1.		 acetylenic ketone acetylenic ketone acetylenic ketone	a. R=CH_2OCH_3 (34%) b. R=$CH(OCH_2CH_3)_2$ (35%) c. R=H d. R=CH_3 e. R=Ph^5
2.			a. R=CH_2OCH_3(50%)^c b. R=$CH(OCH_2CH_3)_2$ (47%)
3.			a. R=CH_2OCH_3 (65%)^{c,d} b. R=$CH(OCH_2CH_3)_2$(30%)
4.			a. R=H (51%) b. R=CH_2OCH_3 (68%) c. R=$CH(OCH_2CH_3)_2$(73%)

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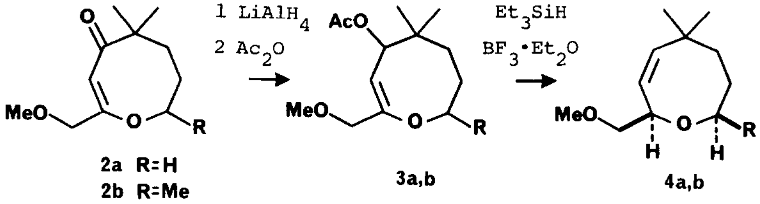
a. yields are not optimized and refer to materials purified by flash chromatography[8]. b. All products are characterized by their UV, IR, MS, ^1H NMR (250 or 500 MHz), and ^{13}C NMR (62.9 or 22.5 MHz) spectra. c. Comparable yields of products can be obtained by the use of RC≡CK (from $KN(TMS)_2$ and RC≡CH) and 18-cr-6. d. based on 70% conversion of lactone.

Experimental To a 1.0 M solution of the acetylene (1.1 eq, 1-10 mmoles) in THF is added dropwise 1.0 eq of n-butyllithium (2.6 M in hexanes) at -78°C. After stirring for twenty minutes, the solution of alkynyl lithium reagent is transferred *via* a steel canula to a solution of the lactone (1 eq, 0.1 M) in THF at -78°C and stirred for one hour. The cold bath is removed and the mixture is allowed to warm to room temperature. Following dilution with THF (50 ml) and HMPA (8 eq), the solution is stirred at room temperature for 3-5 hours. The reaction is quenched with a saturated solution of NH_4Cl, taken up in 50% hexane-ether, washed with saturated $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography of the crude product with 33% ether-hexane provided pure samples of oxocenone. The results of selected examples are summarized in the Table.

α,α-Disubstitution on the δ-lactone is not a requirement for ring expansion, but the lack of substitution leaves the reaction dependent on the nature of the acetylide. δ-Valerolactone reacted with ethynyl and propynyl anions to give addition only but with 1-lithio-3-methoxypropyne or 1-lithio-3,3-diethoxypropyne, oxocenone formation was observed. The α,α-disubstituted lactones underwent addition and ring expansion with each of the acetylide anions that were studied; the dithiomethyl ketal lactone (entry four) reacted with the greatest efficiency. With the exception of this latter example, *the presence of HMPA was necessary for ring expansion to occur*. In one case (entry two) 2 equivalents of HMPA were added to the reaction mixture at room temperature after addition had occurred (-78°C) which immediately caused oxocenone formation to take place. Similarly, the addition product, which could be isolated by quenching the reaction (without HMPA) at -78°C,[5] was cyclized to the oxocenone after being treated with one equivalent of n-butyllithium and 2 equivalents of HMPA at room temperature. In cases where the potassium acetylide was employed, cyclization to the oxocenone required the presence of 18-crown-6.



2a R=H
2b R=Me

3a,b

4a,b

Application of the ring expanding reaction to the synthesis of laurencin and related congeners may be facilitated by a method for reductive transposition of the vinylogous ester to the corresponding allylic ether. A transformation of this description in the dihydropyrone series has been reported by Barrett and co-workers[9,10] in which a 4-hydroxy-5,6-dihydropyran intermediate underwent a Ferrier type olefin transposition[11] with hydride serving as the nucleophile. In order to investigate the feasibility of this reactivity pattern in the eight-membered ring system, the allylic acetates **3a,b** were prepared (88-91% yield). Treatment of **3a** with $BF_3 \cdot OEt_2$ and Et_3SiH in CH_2Cl_2 (-20°C) for fifteen minutes followed by quenching with saturated aqueous $NaHCO_3$ solution[12] provided the transposed oxocene **4a** in 80% yield. Similar treatment of **3b** (as a 4:1 mixture of diastereomers) produced a single cis oxocene **4b** (≥20:1 stereoselectivity)[13] in 83% yield. The diastereoselection in the reduction of **3b** may portend to useful stereochemical control in oxocene functionalization reactions, and is the subject of future investigations in this laboratory.

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13. The cis stereochemistry was assigned on the basis of NOE experiments. For example, irradiation of the C_2 methine proton in **4b** (δ4.31, 500 MHz) resulted in an enhancement of 26% of the C_8 methine proton at δ3.68.

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