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SYNTHESIS AND REACTIVITY OF ENDOCYCLIC α, β-EPOXY-γ-BUTYROLACTONES

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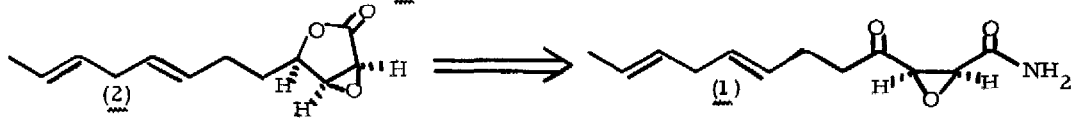
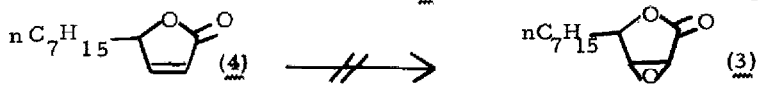
In the course of our studies toward the total synthesis of the fungal metabolite Cerulenin (1),[1] we required α, β-epoxy γ lactone (2) as a key intermediate.



A review of the literature revealed that endocyclic α, β-epoxylactones such as 2 had not been prepared previously. This class of substances could have quite interesting biological activity in their own right, since these substances could function as bifunctional alkylating-acylating agents bycleavage of both the lactone and epoxide by nucleophiles. This possibility would permit them to act as cross linking agents in biological systems.[2]

Consequently, we set out to develop a general method for the preparation of α, β-epoxy-γ-lactones and to study their reactivity with typical nucleophiles. The results of our studies are reported below.

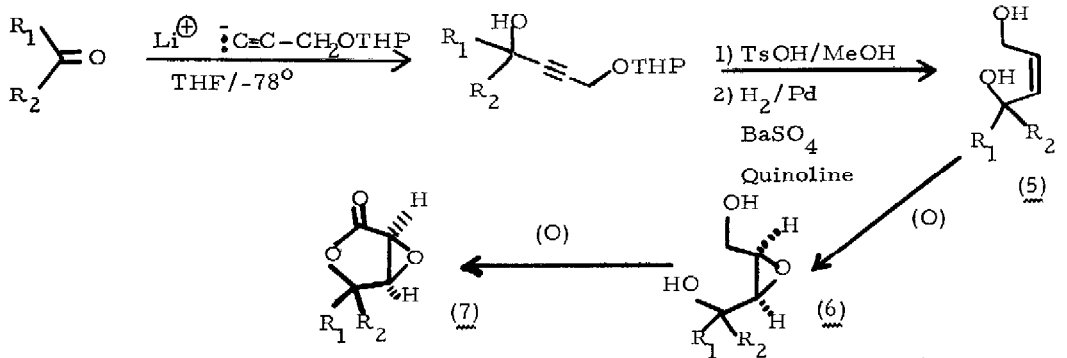
The most direct route to lactones such as (3) is simply epoxidation of the corresponding unsaturated lactone (4). However, an extensive investigation of a variety of oxidizing agents[3] proved uniformly unsuccessful. Lactones such as (4) are inert to all common peracids and



weakly basic peroxide reagents. Use of strongly basic hydrogen peroxide results in isomerization to the δ ketoacid.

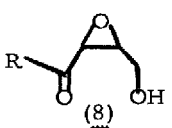
The general route indicated in Scheme 1 was adopted since variation of aldehyde or ketone could provide a number of structurally diverse derivatives. The cis epoxy diols (5) were produced by addition of litho propargyl alcohol THP ether in THF at -78°, followed by removal of the protecting group and catalytic reduction utilizing poisoned Pd/$BaSO_4$.[4] Overall yields

Scheme 1



ranged generally between 45-55% as shown in Table 1. Oxidation to the epoxides (6) was accomplished by treatment with m-Cl $C_6H_4CO_3H$ in CH_2Cl_2 or t-BuOOH/$VO(acac)_2$[5] in cases where double bonds were present. Epoxidation occurs primarily from the side of the double bond that is cis to the secondary alcohol in a ratio of ~7:1, cis to trans.[6] This is to be expected as allylic hydroxyl groups have been shown to direct the stereochemistry of epoxidation of the adjacent double bond.[7,8] Selective epoxidation with peracid failed due to the deactivation of the cis double bond by two hydroxyl groups.[9]

Direct oxidation of diols (6) with most oxidizing agents would be unlikely to produce the desired lactones (7) due to the more rapid oxidation of the secondary hydroxyl.[10] Even though Fetizon showed that Ag_2CO_3/celite oxidized secondary alcohols more rapidly also, lactones were produced in sizable quantities depending upon solvent.[11] We applied this method to the series of epoxydiols (6) and found that generally good to excellent yields of the corresponding epoxy lactones were produced. The minor product in each case was the keto alcohol (8). These substances could be reduced ($NaBH_4$) and reoxidized providing overall a quite efficient conver-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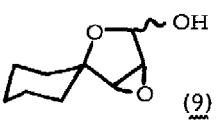
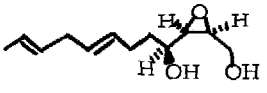
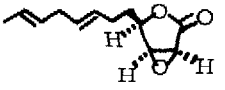
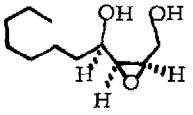
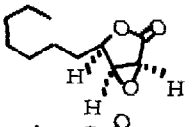
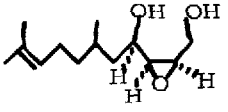
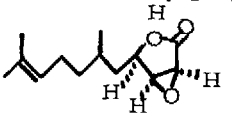
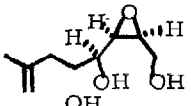
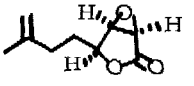
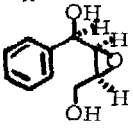
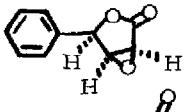
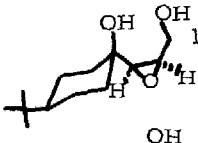
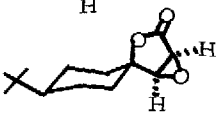
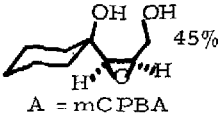
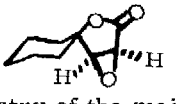

(9)

sion. The ketols (8) are not further oxidized to keto acids and are not in equilibrium with the lactones (7) as is shown by their stability to resubjection to the reaction conditions. Some variability of the oxidation by Ag_2CO_3/celite with respect to structure (of entries 4, 5, Table 1) led us to investigate another method for oxidation of the diols (6) to lactones. Selective oxidation of primary alcohols by Pt/O_2 is well documented in sugar chemistry[12] and has been applied in one case to lactone formation.[13] We have found that this method works quite well in some cases; however, it too shows unexplainable variations with substrate structure. In this case, the presence of double bonds in the side chain appears to result in undesirable side reactions. The only case which led to poor yields for both methods was entry 4. This may be due to isolation problems such as water solubility or volatility. Both aqueous acetone and octane were

employed successfully as reaction media for the Pt/O_2 oxidations with the former generally preferable. As was observed previously,[13] $NaHCO_3$ (~10 eq) enhances the rate of oxidation; however, in some cases, cleavage of the epoxide and hydrolysis were observed when prolonged reaction times (48 hr) were required for complete consumption of starting materials. The oxidation was shown to proceed via the intermediate lactol which was isolated and characterized in the case of entry 7 (Table 1) (9). Production of the lactol is rapid relative to further oxidation to the lactone.

TABLE 1

epoxy diol[1]	yield	method of epoxidation	epoxy lactone	Ag_2CO_3/celite (yield)[2,3,4]	Pt/O_2 (yield)[2,3]
	45%	B		40-60%	20%
	45%	A		60%	70%
	45%	B		50%	30%
	45%	B		20%	--
	55%	A		trace	50%
	15% of one diastereomer	A		80%	90%
	45%	A		70%	40%

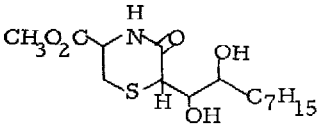
A = mCPBA
B = $tBuOOH/VO(acac)_2$

1) Stereochemistry of the major diastereomer present to the extent of ~7:1 in the crude diol epoxides.
2) Isolated yields purified by chromatography on SiO_2.
3) Characterized by IR, NMR, MS (High and Low Resolution) and elemental analysis (where appropriate).
4) The remainder of the material isolated was the corresponding keto alcohol in 1°, 2° cases.

A typical procedure for the most generally applicable method Ag_2CO_3/celite is as follows: Epoxydiol (entry 1, Table 1) (1.3 g; 6.2 mmol) and 53 g (93 mmol) Ag_2CO_3/celite[14] in 400 ml of benzene were refluxed for 1.5 hr. The solids were filtered, washed with a total of 1,000 ml CH_2Cl_2 and the solvent removed by evaporation. The epoxy lactone was isolated after silica

gel chromatography as a colorless oil bp. 120° at .5 mm (IR: 1780, 1190 and 975 cm^{-1}, neat; NMR: δ 2.8 (m, 2H), 3.76 (d, 1H), 4.1 (m, 1H), 4.5 (m, 1H), 5.5 (m, 4H), $CDCl_3$).

We have exposed the model epoxy lactone (3) to various nucleophiles. The lactone is cleaved by methoxide ion and butyl amine at room temperature but is unreactive to methanol or heptanethiol. Treatment with butyl amine under more vigorous conditions as well as heating in aqueous acetone cleaves the epoxide (but not the lactone in the latter case). Heptanethiol anion also cleaves the epoxide selectively. The potential for crosslinking, which could provide information on the spatial relationships of amino acid residues in proteins and enzymes, is shown by



(10)

the reaction of 3 with cysteine methyl ester affording lactam 10. (IR (cm^{-1}): 3400, 2900, 1740, 1600, 1540) (NMR (δ): 3.9 (s, 3H OCH_3), 3.3 (d, J=6 Hz, 2H CH_2-S) (Mass Spec: M^+=315 (m-18).

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2) These agents should be much less reactive (selective) than the commonly used diazo and halo ketones and esters.
3) Among the reagents tried were MCPBA (w/wo radical inhibitors), CF_3CO_3H/CH_2Cl_2, $NaWO_4/H_2O_2$, tBuOOH/Triton B, $PhCN/H_2O_2$, and $NaOH/H_2O_2$.
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6) The isomers of the epoxy lactones were assigned on the basis of NMR coupling constants. The compounds indicated, alkyl group-epoxide, cis, had coupling constants (J~3 Hz) for epoxide protons and (J~2Hz) between γ-lactone proton and β epoxide proton. The isomer not pictured, alkyl group-epoxide, trans, had coupling constants (J~3 Hz) for epoxide protons and no coupling between γ lactone protons and β epoxide proton, which is expected due to the dihedral angle, as measured from models, by a Karplus correlation.
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9) It is not commonly recognized that an allylic hydroxyl deactivates the double bond to epoxidation. With one hydroxyl group the effect of hydrogen bonding overcomes the deactivation; however, with two hydroxyl groups, isolated double bonds react more rapidly.
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