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THE ADDITION OF CARBANIONS TO IODOLACTONES: A STEREOCHEMICALLY CONTROLLED APPROACH TO SUBSTITUTED TETRAHYDROFURANS

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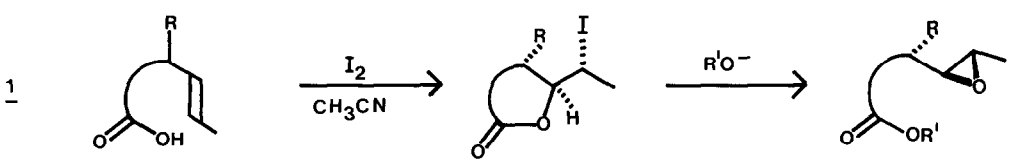
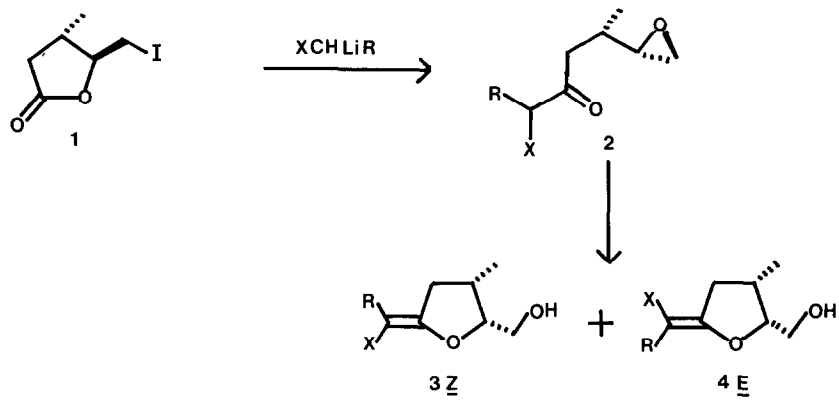
Abstract: The addition of stabilised carbanions XCHLiR to iodolactones (1) give the tetrahydrofurans (3) and (4), potential intermediates in the synthesis of the ionophore antibiotics.

Many natural products, including several important antibiotics, contain tetrahydrofuran fragments, e.g. monensin,[1] nonactin,[2] lasalocid A[3] and M139603[4]. The synthesis of these natural products usually requires the production of such fragments with both the correct relative and absolute stereochemistry as well as suitably placed functional groups to allow incorporation into the synthetic scheme. This communication details some of our preliminary work on the synthesis of such tetrahydrofurans from readily available optically active precursors.

Stereoselective iodolactonisation, followed by the addition of alkoxide (eqn.1), is a valuable method for the stereocontrolled formation of epoxy-esters[5] and one which has found use in the synthesis of several natural products[6]. We have found that the carbanions XCHRLi (X = carbanion stabilising group) will add directly to the iodolactones (1) to give the epoxides[7] (2) which under the reaction conditions[8] ring close to the tetrahydrofurans (3) and (4).



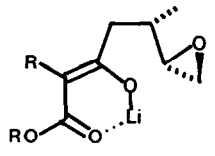


Carbanion XCHLiR	Combined Yield %	Product Ratio (3)	Product Ratio (4)
$PhSO_2CH_2Li$ a	80	3.5	1
Ph_2POCH_2Li a	70	4	1
$LiCH_2CO_2Et$ b	60	5	1
$CH_3CHLiCO_2Bu^t$ b	65	5	1
$CH_3CHLiCN$ b	70	1	3

(a) 2.2 equivalents of the carbanion, generated using n-BuLi, were used;

(b) 4 equivalents of the carbanion, generated using LDA, were used.

A mixture of E and Z isomers[9] is obtained which can be readily separated by column chromatography. In the cases where X is an oxygen based electron withdrawing group, the Z isomer is formed preferentially; however it is known that in similar systems[10] the E isomer is the thermodynamic product. The kinetic preference for the Z isomer probably arises because the intermediate anion (5) has the Z configuration due to lithium coordination to two oxygen atoms. In the case where this coordination cannot occur, e.g. in the reaction using $CH_3CHLiCN$, the E isomer predominates. We have shown that the Z isomer (3, $X=CO_2Bu^t$, $R=CH_3$) can be converted in high yield to the E isomer (4, $X=CO_2Bu^t$, $R=CH_3$), (E:Z 4:1) using sodium ethoxide in ethanol. Thus, either the E or Z isomer can be obtained stereoselectively.



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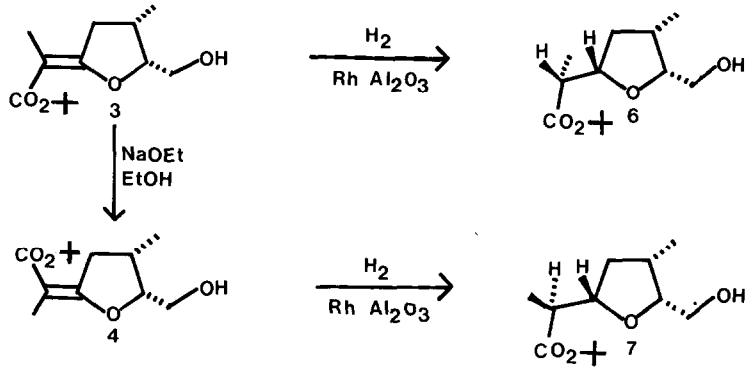
It is known that tetrahydrofurans such as (3) can be hydrogenated from the less hindered face.[11] We have shown that the isomers (3, $X=CO_2Bu^t$, $R=CH_3$) and (4) can be reduced to give a single isomer in each case which, by analogy, should have the relative stereochemistry shown in (6) and (7). Furthermore, since the iodolactone (1) can be obtained in optically pure form,[12] it should be possible to control not only the relative, but also the absolute stereochemistry, at the four centres in the tetrahydrofurans (6) and (7). The application of this work to the synthesis of the ionophore antibiotics will be reported at a later date.



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7. The epoxides (2) can be isolated by quenching the reaction mixture at low temperature with ammonium chloride solution.
8. Given below is a typical reaction procedure.

Preparation of (3/4 $X=CO_2Bu^t$, $R=CH_3$). - To a solution of t-butyl propionate (520 mg, 4 mmoles) in THF (5 ml) at -78° C under nitrogen was added LDA (4 mmoles in 1.5 ml THF) over a period of 10 min. After 30 min at -78° C the iodolactone (1) (240 mg, 1 mmole) in THF (3 ml) was added and the mixture stirred at -78° C for 1 h. The mixture was then allowed to warm to room temperature and after stirring for 18 h was poured into ammonium chloride solution and extracted with dichloromethane (3 x 20 ml). The extracts were washed with water (20 ml), brine (20 ml), dried over magnesium sulphate and the solvent removed under reduced pressure. The resulting oil contained (3, $X=CO_2Bu^t$, $R=CH_3$), (4, $X=CO_2Bu^t$, $R=CH_3$) and the self-condensation product of t-butyl propionate. These were separated by flash column chromatography using 4:1 ethyl acetate:petroleum ether (b.p. 60-80°) as eluant.

9. The E and Z stereochemistries were assigned by comparing the chemical shifts and coupling constants for the allylic CH_2 and vinyl proton (or methyl group) with known systems (see ref.10).
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