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A ROUTE TO PRELOG-DJERASSI LACTONE FROM METHYL α,D-GLUCOPYRANOSIDE

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SUMMARY: *The enone 1 obtainable from methyl α,D-glucopyranoside is converted into the corresponding diene 5 which is hydrogenated to give predominantly the diequatorial dimethyl hexopyranoside 3. C6 of the latter is converted stepwise to the methyl ketone from which Prelog-Djerassi Lactone 8 and its 2-epimer 9 are prepared in 3:2 ratio.*

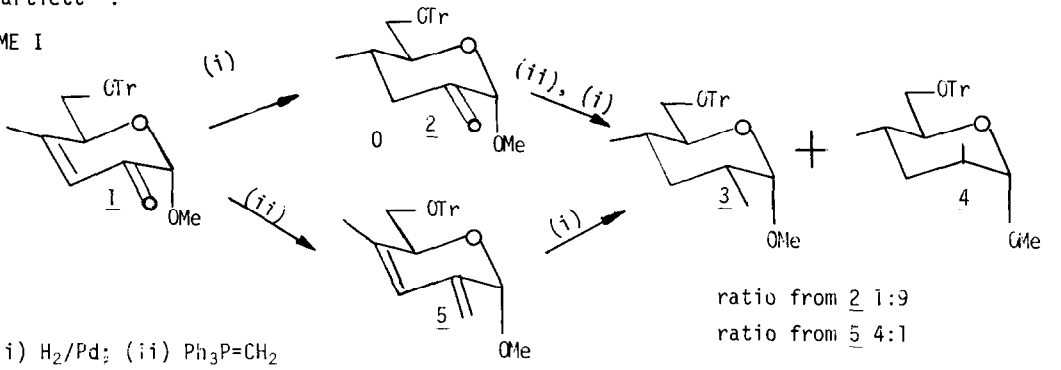
Prelog-Djerassi lactone 8 has been a focus of attention since its isolation as a degradation product of narbomycin and methimycin[2,3]. Its importance for macrolide construction was first demonstrated by Masamune in his synthesis of methimycin[4], and since then there have been a number of preparations of 8, usually in racemic form[5]. A notable exception is Masamune's synthesis of (+)8, which employs his methodology for stereoselective aldol condensations of acyclic systems. Ireland and Daub have recently reported a carbohydrate-based synthesis in which the side chain configurations were controlled by an Ireland-Claisen rearrangement[6]. In this communication we outline an entirely different approach beginning with methyl α,D-glucopyranoside.

The drawing of 8 in the $^4C_1$ conformation (Scheme III) indicates its absolute configurational relationship[7] to methyl 2,3,4-trideoxy-2,4-C-dimethyl-α,D-ribo-hexopyranoside,3, diastereomers of which have been of interest in connection with our work on the multistriatins[8]. In this study 3 had been obtained as the minor product in the hydrogenation of 2, and our first objective was therefore to develop an improved route for its preparation.

Hydrogenacion of enone 1[8] gave the equatorial C4 methyl ketone 2 exclusively. We reasoned that enone 1 and diene 5 should occupy the same conformation, and that hydrogenation of the latter would therefore favour formation of 3. Indeed hydrogenation of 5[9] gave 3 and 4 in the ratio 4:1 (NMR estimation)[8], and prolonged hydrogenation cleaved the trityl group, the resulting alcohols being separated by column chromatography.

With regard to the desired C2 arrangement of 8, we had hoped that the pyranoside ring would induce stereoselectivity in reactions occuring at a trigonal centre at C6 of suitable precursors. The epimeric mixture (8 and 9) that would result had been previously prepared by Bartlett[5a].

SCHEME I



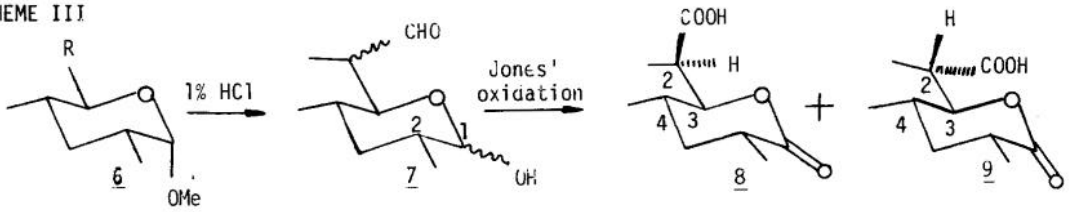
The alcohol 6a was oxidized to the aldehyde 6b (PCC[10], CH_2Cl_2, 12 h, 85%) and we tried to apply the "one pot" geminal alkylation procedure of Martin and co-workers (Scheme II)[11] for preparing the homologue 6c, but unfortunately we were unsuccessful. The ketone 6d was

SCHEME II

RCHO {PCH=CH-N=CHPh} $RCH(CH_3)COOR'$ reference 11

therefore prepared from 6b ((i) MeLi, (ii) PCC) and treated with $Ph_3P{=}CHOMe$[12]. Stirring with 1% aqueous hydrochloric acid simultaneously hydrolyzed the enol ether product and the glycosidic methoxyl giving 7, there being no evidence of eperimizations at C2. Jones' oxidation of 7 gave a mixture of Prelog-Djerassi lactone, 8, and its 2-epimer 9 in 3:2 ratio, the overall yield from 6d being 47 percent. The configurations of the isomers were assigned on the basis of the H3 PMR signals at 4.70 ppm for 8 and 4.17 ppm for 9 which compare favorably with those (4.59 and 4.17 respectively) for the racemic modifications reported by Bartlett[5a].

SCHEME III



a CH_2OH
b CHO
c $CH(CH_3)CHO$
d $COCH_3$

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9. Diene 3 was prepared from 1[7] in 74% yield by a standard Wittig reaction done in benzene at room temperature. NMR: 5.98s (H-3), 5.25s (H-1), and 4.88s (2H = CH_2); m/e: 349 (M^+ - Ph·), 183 ($M+Ph_3C$·), 167 ($M-Ph_3CO$·).
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