The Synthesis of the δ-Lactone Portion of the Mevinic Acids; a New Non-acidic Method of Cyclic Lactone Expansion

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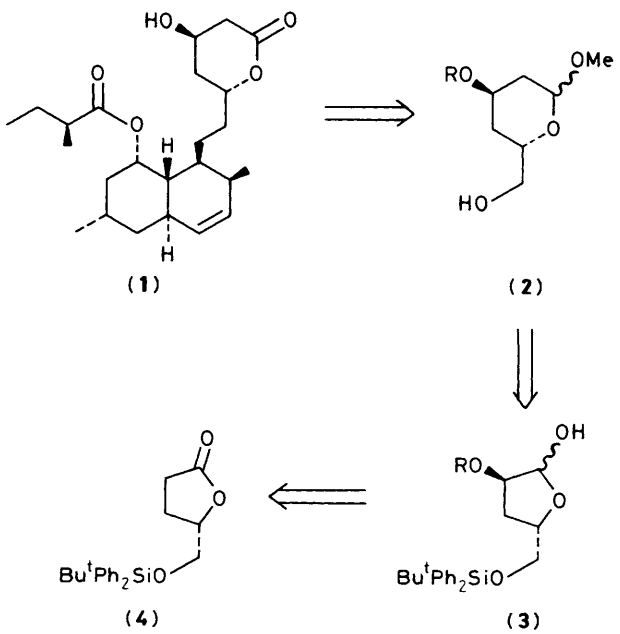
An alkoxy-mercuration demercuration sequence has been used as the key step in an enantiospecific synthesis of a protected synthon for the lactone portion of the mevinic acids.

As part of our synthesis[1] of the hypocholesterolaemic agent, dihydromevinolin (**1**), we required an enantiospecific route to a protected form of the lactone portion,[2] represented by (**2**) (Scheme 1). It was thought that this would be accessible by a one carbon ring expansion of the lactol (**3**). This in turn could be derived from the readily available,[3] optically pure lactone (**4**) which we used for the synthesis of the octahydronaphthalene portion of dihydromevinolin.

The transformation (**4**) to (**5**) was achieved using lithium hexamethyldisilazide (LiHMDS) and MoOPH, the method of Hanessian,[3] and gave good stereoselectivity (9 : 1) in favour of the *trans* form of (**5**). Protection of the alcohol as the $MeO(CH_2)_2OCH_2$ (MEM) ether‡ gave (**6**) in 84% yield (Scheme 2). Once the desired relative and absolute stereochemistry had been established, all that remained was to expand the ring, using a one-carbon Wittig reagent with appropriate functionality. However, the ylid derived from 1,3-dithian-2-yltriphenylphosphonium chloride[4] failed to react with the lactol obtained by di-isobutylaluminiumhydride (DIBAL) reduction of (**4**), and use of the methoxy- or trimethylsilylethoxy-methylenetriphenylphosphoranes gave



Scheme 1

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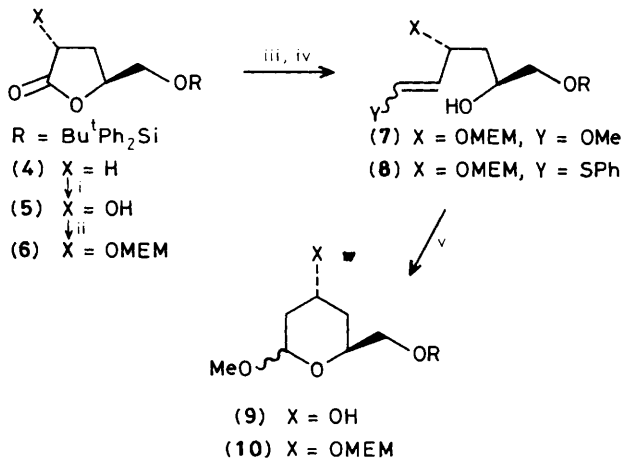
poor yields (30—40%). Moreover, treatment of the enol ether (**7**)‡ with pyridinium *p*-toluenesulphonate in methanol gave material resulting from elimination of the allylic hydroxy group.

In contrast to the above results, phenylthiomethylenetriphenylphosphorane[4] reacted with the the lactol from (**6**) to give the vinyl sulphide (**8**) as a mixture of geometric isomers in 84% yield.‡ Attempted hydrolysis of the vinyl sulphide using standard mercury reagents, or other direct methods,[4,5] led to elimination or extensive decomposition. The required transformation was eventually carried out by alkoxy-mercuration of the double bond in (**8**) using mercury(II) acetate in methanol buffered with mercury(II) oxide, and treating the resulting solution with excess sodium borohydride. Extractive work up and chromatography gave both anomers of the tetrahydropyranol (**10**) in a combined yield of 70%.‡§ The same procedure was used to ring expand the unprotected material (**5**) to (**9**),‡ but yields were lower. This appears to be the first instance of an alkoxy-mercuration demercuration sequence being used to hydrolyse a vinyl sulphide with concomitant ring closure,[6] and should be a useful method for other systems containing acid sensitive functionality.

In summary, we have described a novel, enantioselective synthesis of a key intermediate in mevinic acid syntheses, which utilises a new method for the hydrolysis of alkoxyvinylsulphides to lactols.



Scheme 2. *Reagents and conditions*: i, LiHMDS, THF, MoOPH −78 °C; ii, NaHMDS, THF, MEMCl −78 °C, iii, DIBAL, THF, −78 °C; iv, PPh_3=CH–Y, THF, −78 °C to r.t.; v, $Hg(OAc)_2$, HgO, MeOH, $NaBH_4$.

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‡ All new compounds gave satisfactory microanalytical or mass spectral data.

§ Selected spectroscopic data and experimental details for (**10**): the vinyl sulphide (**8**) (170 mg, 0.30 mmol) was dissolved in dry methanol (5 ml), mercury(II) acetate (230 mg, 0.72 mmol) and mercury(II) oxide (167 mg, 0.77 mmol) were added, and the suspension was stirred vigorously for 20 h under nitrogen. An aqueous solution of sodium borohydride (1 M) and sodium hydroxide (1 M) (3 ml) was added in one go, and the resulting grey mixture stirred for 30 min. Extraction with ether, and flash chromatography gave (**10**). Major anomer; $[\alpha]_D$ −40.6° (*c* 1.86, $CHCl_3$); ^{1}H n.m.r. (360 MHz, $CDCl_3$) 7.8—7.7 (4H, m), 7.5—7.3 (6H, m), 4.80 (2H, s), 4.70 (1H, dd, *J* 2, 10 Hz), 4.20 (1H, quintet, *J* 3 Hz), 3.98 (1H, dtd, *J* 11, 6, 2 Hz), 3.82 (1H, dd, *J* 10, 6 Hz), 3.72 (2H, m), 3.66 (1H, dd, *J* 10, 6 Hz), 3.56 (2H, m), 3.50 (3H, s), 3.40 (3H, s), 2.0 (1H, m), 1.85 (1H, m), 1.56 (1H, m), 1.45 (1H, m), 1.08 (9H, s); ν_{max} 2940, 1590, 1430 cm^{-1}.

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