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A Flexible Synthesis of Some Polysubstituted Cyclopentanes From Quinic Acid.

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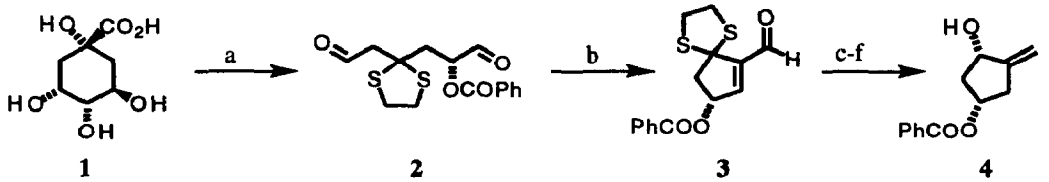
Abstract: Quinic acid is converted stereoselectively into a common cyclopentane intermediate useful for the synthesis of carbocyclic nucleosides prostaglandins and other important cyclopentane based compounds.

Quinic acid **1** has recently become of interest as a starting material for organic synthesis. Most of these applications have been to the synthesis of cyclohexane derivatives[1-10], some applications to the synthesis of linear molecules[11,12] and also to cyclopentane derivatives as prostaglandin analogues. The biological activity of cyclopentane derivatives as antiviral agents has again highlighted their importance in medicine. The carbocyclic nucleosides have proven to be effective against various viral infections including the HIV which causes AIDS[13].

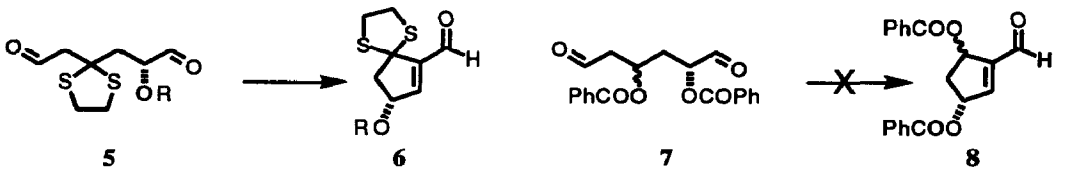


1 **2** **3** **4**

Scheme 1. (a) See references 1 to 10 and 12. (b) pyrrolidine acetate (c) $NaBH_4$, EtOH, 2h, 25°C, 95%. (d) BzCl, pyridine, DMAP, 1.5h, 25°C 98%. (e) $(PhSeO)_2O$, propylene oxide, 18h, 25°C, 82% (f) $NaBH_4$, EtOH, 1h, 0°C, 95%.

We present here our results on the synthesis and manipulation of cyclopentane derivatives elaborated from quinic acid, which serve as common precursors for prostaglandins, carbocyclic nucleosides and a variety of polysubstituted cyclopentanes. The overall process is summarised in scheme 1. We retain all possible functionality available from quinic acid, which had not been achieved during previous syntheses[14] using these derivatives. The key intermediates in this scheme are the aldehyde **3** and the exocyclic olefin **4** which are formed in good overall yield and with complete control of stereochemistry. Our strategy is based upon the regioselective1,4-addition of hydrogen to a cyclopentenone using borohydride followed by elimination and a highly diastereoselective reduction of the resulting α,β-unsaturated ketone to form a hydroxycyclopentane with an exocyclic double bond which is amenable to a variety of selective functionalisation reactions.

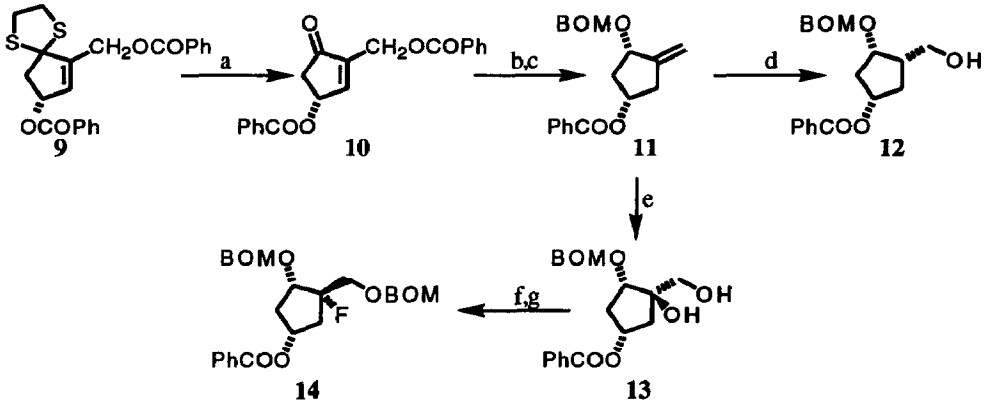
The cyclopentencarboxaldehyde unit **3** $[\alpha]_D^{20}$= +259.8 (c=1.36, CH_2Cl_2) is prepared in good overall yield from quinic acid **1** by a route similar to but more efficient than that described in the literature[14]. Since a key step



5 6 7 8

Scheme 2.

in this route is the conversion of dialdehyde **2** to the the cyclopentene **3** we have studied the scope of this transformation. Cyclisation of the precursor dialdehydes **5** to give cyclopentenes **6** has only been acheived when using a primary or secondary amine based catalyst (salt or free base) and when the dialdehyde contains the dithioacetal group. A protected secondary alcohol **7** instead of the dithioacetal at the corresponding centre, produced very little recognisable product and none of them cyclopentenes. This may be due to elimination at the β-position with respect to the aldehyde group which is a fairly easy process under the reaction conditions, however, the corresponding dithiane also does not cyclise as does the dithiolane. These results indicate that a dithiolane, or other five membered ring system, is necessary for efficient cyclisation. The dithiolane probably helps the two reacting centres to attain the necessary conformation and proximity for efficient cyclisation. If this situation is not rapidly achieved then polymerisation probably occurs. This hypothesis is supported by the fact that if cyclisation does not occur, virtually only a black tarry mixture is recovered and is probably oligomeric material. The results of a larger study of this reaction will be published in due course but it is evident that this cyclisation is probably not as straightforward as it initially appears.

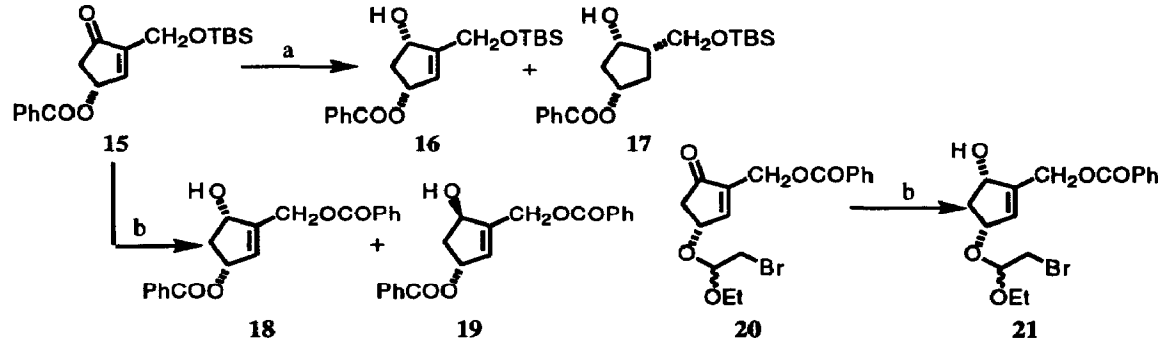


9 10 11 12 13 14

Scheme 3. (a) $(PhSeO)_2O$, (b) $NaBH_4$, EtOH, (c) BOMCl, i-Pr_2NEt, (d) i) 9-BBN, ii) NaOH, H_2O_2, (e) OsO_4, NMO, (f) BOMCl, i-Pr_2NEt, (g) DAST.

The reduction of the resulting aldehyde **3** with sodium borohydride furnished the primary alcohol exclusively with no 1,4-reduction occurring. After protection of this hydroxyl as its benzoate (compound **9** $[\alpha]_D^{20} = +76.8\pm0.1$, (c=0.88, CH_2Cl_2)) attempts were made to remove the dithioacetal protecting group. With several metal based reagents we were unsuccessful and this transformation could only be acheived efficiently with

phenylseleninic anhydride[15].The product **10** was again treated with borohydride in ethanol at 0°C in the hope of reducing the carbonyl group stereoselectively.We expected that perhaps 1,4-reduction would also occur as is frequent in the reduction of cyclopentenones to give a saturated system as a mixture of diastereoisomers. The reaction however proved to be extremely selective and compound **4** $[\alpha]_D^{20}$ = +33.7, (c=2.67, CH_2Cl_2) was formed almost exclusively. Significant quantities of its epimer were produced only when the reduction was carried out above 10°C. Obviously the hydride attacks in a 1,4-manner and the enolate formed eliminates benzoic acid. This type of addition elimination has previously been observed on adding alkyl group in a 1,4-fashion. Finally the new α,β-unsaturated ketone formed is reduced 1,2- and diastereoselectively to produce the observed product. A comparison of the nmr of the dibenzoates of **4** and its epimer indicated the relative stereochemistry of the two ester groups attached to the ring. As a general rule the *syn*-disubstituted cyclopentanes show greater separation of the diastereotopic methylene protons between the hydroxyl groups, than the corresponding *anti*-diastereoisomer. An X-ray structure determination of the dibenzoate of **4** (figure 1) confirmed our analysis and so we are able to assign the absolute configuration at both asymmetric centres, one of them having been retained from quinic acid.



Scheme 4. (a) $NaBH_4$, EtOH, (b) $NaBH_4$, $CeCl_3$, EtOH.

The borohydride reduction of compound **15**, $[\alpha]_D^{20}$ = +58.4, (c=1.30, CH_2Cl_2) which was derived from the corresponding dithioacetal by reaction with phenylseleninic anhydride (75%), resulted in a mixture of 1,2- (37%) **16** and 1,4- (50%) **17** reduction products. No exocyclic elimination occurred as expected and the products were all *cis*-. In the presence of cerium(III)/borohydride[16] only the expected 1,2-reduction of **15** occurred but with low diastereoselectivity (55% **18** cis-, 32% **19** trans-). Compound **20** $[\alpha]_D^{20}$ = +26.8, (c=0.96, CH_2Cl_2), a mixture of diastereoisomers at the mixed acetal function, on the other hand, was reduced by cerium (III)/ borohydride with a selectivity of >95:5 in favour of the cis-ring substituted isomer **21**, 98% $[\alpha]_D^{20}$ = +24.5, (c=1.51, CH_2Cl_2). We postulate that the cerium is chelated by the mixed acetal group on the lower face of the π-system thus effectively impeding attack to this face of the carbonyl group. The radical cyclisation of compounds related to compound **21** results in bicyclic precursors for prostaglandin synthesis. Studies are underway to determine if this directing effect is shown by other chelating groups. Our experience with related compounds indicate that it is not just a case of steric hindrance.

We now had in hand a variety of derivatives of which compound compound **4** proved to be very versatile. It has two asymmetric centres clearly defined and a π system, one face of which was highly hindered with respect

to the other. Protection of the hydroxyl group as its benzyloxymethyl ether, in order to differentiate the two hydroxyl groups at a later date, afforded key compound **11** which we proceeded to functionalise (scheme 3).

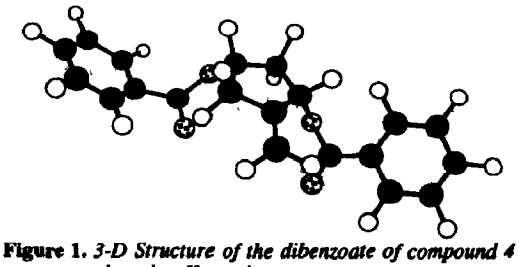


Figure 1. *3-D Structure of the dibenzoate of compound 4 based on X-ray data.*

For example, dihydroxylation using catalytic OsO_4[18] generated the diol isomer **13** 94% $[\alpha]_D^{20}$ = +53.4, (c=1.84, CH_2Cl_2) exclusively. This was then converted into the BOM ether and transformed into the fluoro derivative **14** 57% $[\alpha]_D^{20}$ = +13.0, (c=0.66, CH_2Cl_2) using DAST[19,20], and with complete inversion of configuration. Hydroboration with 9-BBN[17] followed by oxidation afforded primary alcohol **12** with complete stereochemical and regiochemical control.

The enantiomers of compounds **9**, **15** and **20** are all available from a common precursor and via efficient inversion of the chiral centre using Mitsunobu procedures earlier in the synthesis.

A wide variety of optically pure polysubstituted cyclopentanes are available from a common intermediate which is derived from quinic acid. These compounds find application in the synthesis of pseudo sugars, prostaglandins, and cylopentane based cytotoxic (anticancer) agents.

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