The Synthesis of 6-Substituted Shikimic Acids

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6-Hydroxy-, 6-amino- and 6-mercapto-shikimic acids have been synthesised from quinic acid and improved methods developed for the synthesis of the 6-fluoroshikimic acids.

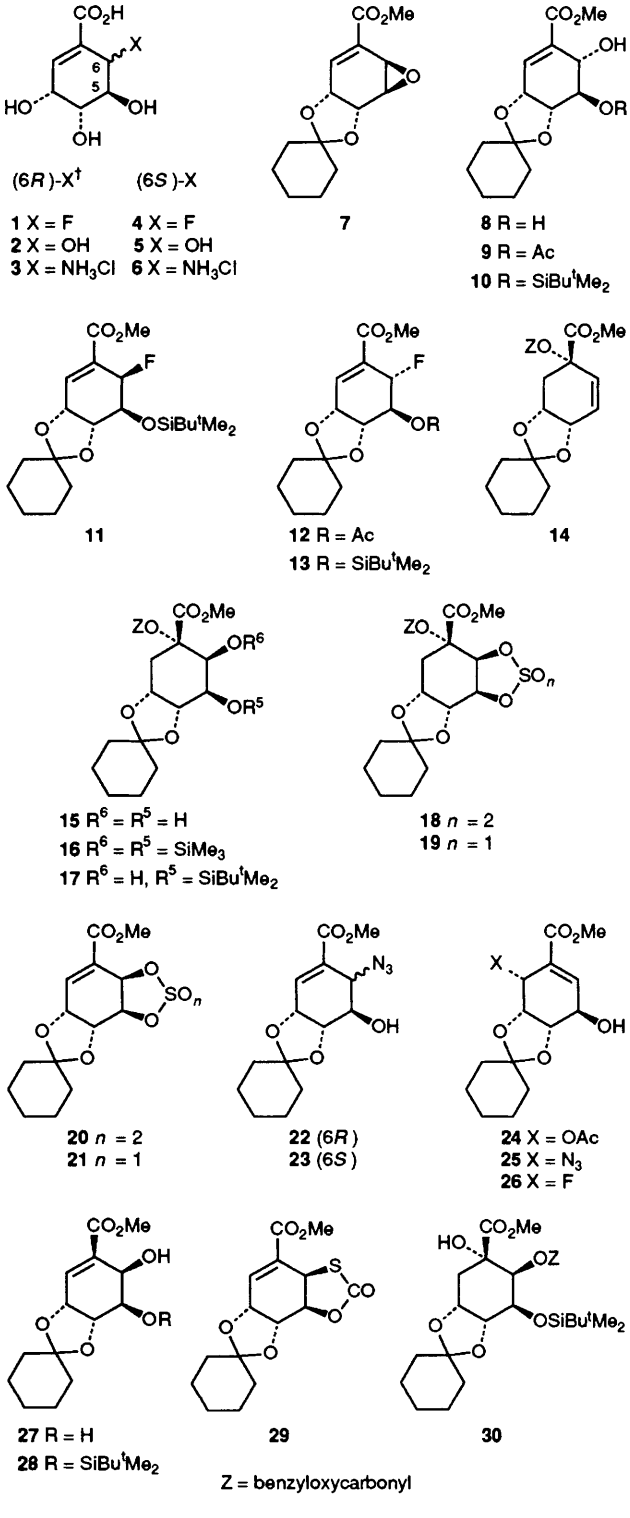
Previously we have described[1] the preparation of (6*R*)- and (6*S*)-6-fluoroshikimic acids **1** and **4**† which have been converted enzymatically into the enolpyruvylshikimic phosphates; these have been shown to be reversible inhibitors of the enzyme chorismate synthase.[2] These results encouraged us to prepare other 6-substituted shikimic acids and to improve the routes to the 6-fluoro compounds.

The epoxide **7** was a key intermediate in our previous synthesis and on hydrolysis (CF_3CO_2H–H_2O–Me_2SO) gave the diol **8** (74%) which was converted into (6*S*)-6-hydroxyshikimic acid **5**‡ (57%) by sequential treatment with MeOH–HCl and 5 mol l^{-1} HCl. Selective acetylation of the diol **8** gave the monoacetate **9** (84%) which on reaction with Et_2NSF_3[3] gave a mixture of the 5- and 6-monoacetates of the *cis*-diol **27** and the (6*S*)-6-fluoride **12** (58%) suggesting that neighbouring group participation of the acetoxy function is involved in the formation of the products. This could be avoided by reaction of the diol **9** with $Bu^tMe_2SiOSO_2CF_3$ (1 equiv.) to give the alcohol **10** (75%) which was converted into the (6*R*)-6-fluoride **11** (64%) on reaction with Et_2NSF_3.

The alkene **14** was also an intermediate in our previous synthesis and on hydroxylation with OsO_4–*N*-methylmorpholine *N*-oxide–Bu^tOH[4] gave the diol **15** (89%) which was converted ($SOCl_2$ then $RuCl_3$–$NaIO_4$)[5] into the sulfate **18** (90%) *via* the sulfite **19**. Hydrogenolysis, followed by dehydration (Et_2NSF_3), gave the sulfate **20** (46%) which reacted[5,6] with NaN_3–Me_2NCHO–tetrahydrofuran (THF) to give, after hydrolysis, a mixture of the azides **22** (71%) and **23** (25%). The azides were separated, reduced[7] (Ph_3P–THF then H_2O), and hydrolysed (MeOH–HCl then 5 mol l^{-1} HCl) to give the hydrochlorides of (6*R*)- and (6*S*)-6-aminoshikimic acids **3** and **6** (39 and 28% respectively). Reaction of the sulfate **20** with Bu^n_4NF–THF gave an inseparable mixture (50%) of the known *epi*-shikimic derivative **26** and a cyclohexadiene which we were unable to identify completely.

Conversion of the quinate sulfites **19** into the shikimate **21** was unsatisfactory, but by altering the order of reactions a satisfactory procedure was developed. Reaction of the diol **15** with Me_3SiCl–Et_3N–CH_2Cl_2 gave the ether **16** which on hydrogenolysis, dehydration {$[PhC(CF_3)_2]_2SPh_2$}[8] and desilylation gave the diol **27** (70%). Reaction of the diol **27** with $SOCl_2$ gave the sulfites **21** (72%) which reacted with Bu^n_4NF to give a mixture of mainly the unknown diene with some *epi*-shikimate **26**. The sulfites reacted[9] with NaN_3–Me_2NCHO at 20 °C to give a 7:2 mixture (90%) of the azides **22** and **23**; however reaction at −15 °C yielded (90%) **22** and the *epi*-shikimic acid azide **25** (1:3) which was stable in Me_2-NCHO at 20 °C, but addition of a catalytic amount of NaN_3 converted it into the equilibrium mixture of **22** and **23**. Hydrolysis of the diol **27** gave (6*R*)-6-hydroxyshikimic acid **2**.

Because of the complexity and unpredictability of the substitution reactions on the previous derivatives we wished to exercise more regio- and stereo-chemical control in the synthesis of the 6-thiol derivative. It is well established that *S*-thioesters are more thermodynamically stable than their *O*-counterparts and that this isomerisation will occur when mechanistically possible. In the event reaction of the diol **27**



† In (6*R*)-compounds the 5- and 6-substituents are *cis*, in (6*S*) *trans*.

‡ Regio- and stereo-chemistry were established by a combination of ^1H NMR spectroscopy, 2D-COSY experiments, molecular modelling, and application of the Altona equation[12] to the relevant compound and its derivatives.

with thiocarbonyldiimidazole–PhMe gave the *S*-thiocarbonate **29** (74%) directly. Hydrolysis gave crude (6*R*)-6-mercapto-shikimic acid.

The successful synthesis of the (6*R*)-fluoro derivative **11** from **10** encouraged us to prepare the epimer **28**. Reaction of the diol **15** with $Bu^tMe_2SiOSO_2CF_3$ (1 equiv.) gave the silyl ether **17** (64%) which on treatment with $NaH–CH_2Cl_2$ underwent a *trans*-transesterification to form the isomer **30** (91%). Dehydration $\{[PhC(CF_3)_2]_2SPh_2\}$ followed by hydrogenolysis gave the alcohol **28** (78%) which reacted with Et_2NSF_3 to yield the (6*S*)-6-fluoro derivative **13** (72%). These are now the preferred routes to the 6-fluoroshikimic acids.

Michael addition to shikimic ester 3,4-ketals occurs from the convex face of the molecule[10] and, taken together with the greater thermodynamic stability§ of the shikimic ketals over those of the *epi*-series, suggests that there must be a stereoelectronic imperative for the unique formation of the (6*R*)-*epi*-stereochemistry in certain substitution reactions; this, we suggest, is an *anti*-S_N2' reaction[11] leading to a kinetic product. Michael addition to the appropriate face of the *epi*-isomers, followed by elimination to generate the more thermodynamically stable shikimic derivatives can then occur leading to (6*R*)- or (6*S*)-derivatives.

§ Chemical evidence and MM2 calculations support this view.

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