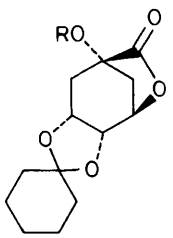
The Synthesis of 6α- and 6β-Fluoroshikimic Acids

James K. Sutherland,[a] William J. Watkins,[a] John P. Bailey,[b] Alison K. Chapman,[b] and Gareth M. Davies*[b]

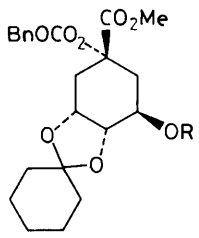
[a] *Chemistry Department, Victoria University of Manchester, M13 9PL, U.K.*
[b] *ICI Pharmaceuticals, Alderley Park, Macclesfield, Cheshire SK10 4TG, U.K.*

6α- and 6β-Fluoroshikimic acids have been synthesised from quinic acid in 14 stages.

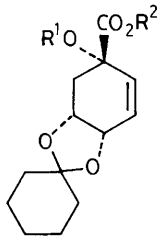
The shikimic acid cycle is of central importance for the biosynthesis of aromatic amino acids in micro-organisms[1] and it was of interest to us to synthesise fluorinated derivatives. The starting material was the readily available quinic acid which was converted to the known lactone (**1**). Reaction of the alcohol (**1**) with NaH–BnOCOCl–Bu_4NI–CH_2Cl_2 (Bn = $PhCH_2$) formed the ester (**2**) (92%) which with NaOMe was converted to the ester (**3**) (81%); this, in turn, reacted with $(CF_3SO_2)_2O$–pyridine–CH_2Cl_2 to give the triflate (**4**) (96%). Elimination of triflic acid with DBU–$CHCl_3$ (DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene) yielded the alkene (**5**) which was hydrolysed (KOH–H_2O–dioxan) to the acid (**6**) and



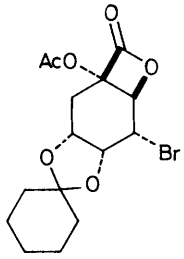
(**1**) R = H
(**2**) R = BnOCO



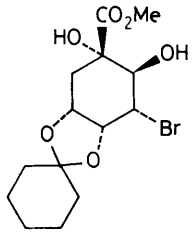
(**3**) R = H
(**4**) R = SO_2CF_3



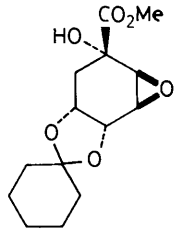
(**5**) R^1 = BnOCO, R^2 = Me
(**6**) $R^1 = R^2 = H$
(**7**) R^1 = Ac, R^2 = H



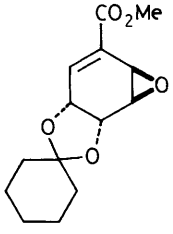
(**8**)



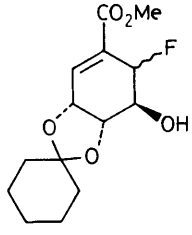
(**9**)



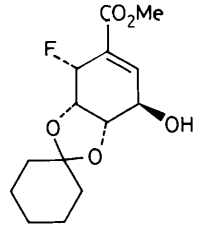
(**10**)



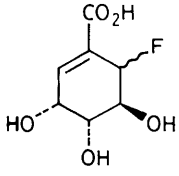
(**11**)



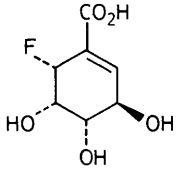
(**12**) α-F
(**13**) β-F



(**14**)



(**15**) α-F
(**16**) β-F



(**17**)

acetylated to form the acid (**7**). Bromolactonisation of the acid (**7**) using $C_5H_6NBr_3$–$NaHCO_3$–H_2O–THF (THF = tetrahydrofuran) gave the β-lactone (**8**) [68% from (**4**)], ν_{max} 1850, 1740 cm^{-1}. Cleavage of the lactone with NaOMe–MeOH also removed the acetate group forming the bromohydrin (**9**) (75%) which was converted to the epoxide (**10**) (82%) using Bu_4NOAc–Me_2NCHO. Dehydration of the epoxide (**10**) proved to be difficult and capricious; after extensive investigation it was shown that the sulphurane,[2] $[PhC(CF_3)_2O]_2SPh_2$, efficiently converted (**10**) to the epoxide (**11**) (87%), δ_H 6.79 (1H, dd, *J* 2.3 and 1.5 Hz), 4.75 (1H, dd, *J* 6.5 and 2.1 Hz), 4.53 (1H, dd, *J* 6.5 and 2.3 Hz), 3.93 (1H, dd, *J* 3.7 and 1.5 Hz), and 3.63 (1H, dd, *J* 3.7 and 2.1 Hz). Reaction of the epoxide (**11**) with HF–pyridine reagent[3] gave a mixture of the epimeric fluorohydrins (**12**) and (**13**) and the regioisomer (**14**) (54% in total). The mixture could be partially purified by silica gel chromatography to give (**12**) (35%), δ_H (C_6D_6) 6.90 (1H, dd, *J* 3.1 and 3.0 Hz), 5.3 (1H, dd, *J* 43.7 and 4.0 Hz), 4.43 (1H, ddd, *J* 5.5, 3.4, and 3.0 Hz), 4.25 (1H, dm, *J* 12 Hz), 4.16 (1H, dd, *J* 5.5 and 5.3 Hz), and a mixture of (**13**), δ_H 7.00 (1H, t, *J* 3.8 Hz), 5.65 (1H, dd, *J* 50.2 and 2.5 Hz), 5.15 (1H, ddd, *J* 25.5, 9.3, and 2.5 Hz), 4.50 (1H, dd, *J* 9.3 and 6.6 Hz), 4.30 (1H, m) and (**14**), δ_H 7.4 (1H, m), 5.75 (1H, dd, *J* 45 and 2 Hz), 4.73 (1H, ddd, *J* 11.6, 6, 4, and 2 Hz), 4.43 (1H, m), 4.40 (1H, dd, *J* 6.4 and 4 Hz), which could be separated by liquid chromatography on a Dynamax C_{18} column. The 6β-fluoroshikimic acid (**16**) was obtained from the ester (**13**) by hydrolysis to the acid (LiOH–H_2O–dioxan) followed by removal of the cyclohexylidine group (CF_3CO_2H–CH_2Cl_2) and purification of the water soluble acid (**16**) by liquid chromatography on Dynamax C_{18} columns (40%). The 6α-fluoroshikimic acid (**15**) was obtained (59%) by removal of the cyclohexylidine group with CF_3CO_2H–CH_2Cl_2 to give the triol and then the ester hydrolysed with 6 M HCl to the water soluble acid (**15**) which was purified by liquid chromatography on a Dynamax C_{18} column. The regioisomer (**17**) was prepared using a similar protocol. The structures and stereochemistry of the fluoro compounds were established by extensive ^1H, ^{13}C, and ^{19}F n.m.r. spectroscopy which will be discussed in the full publication. From these results it is apparent that the epoxide ring opening is not stereospecific presumably due to the intervention of the allylic cation.

We thank the S.E.R.C. and ICI Pharmaceuticals for financial support and H. A. Beeley and B. Wright for the n.m.r. spectroscopy.

Received, 25th April 1989; Com. 9/01740B

References

1 E. Haslam, 'The Shikimate Pathway,' Halstead Press, N.Y., 1974.
2 R. J. Arhart and J. C. Martin, *J. Am. Chem. Soc.*, 1972, **94**, 5003.
3 G. A. Olah, J. T. Welch, Y. D. Vankar, M. Nojima, I. Kerekes, and J. A. Olah, *J. Org. Chem.*, 1979, **44**, 3872.