Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 6, No. 11, pp. 1275-1278, 1996

0960-894X/96 $15.00 + 0.00

PII: S0960-894X(96)00215-6

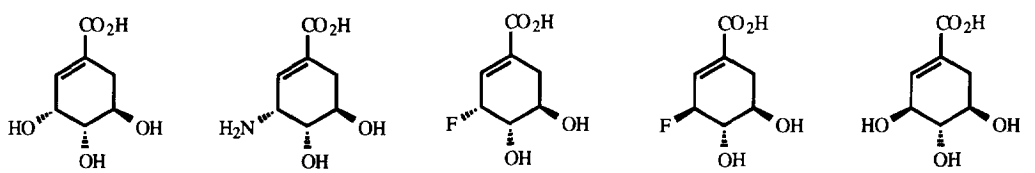
SYNTHESIS OF (3*R*)- AND (3*S*)-FLUORO-(4*R*,5*R*)-DIHYDROXY-1-CYCLOHEXENE-1-CARBOXYLIC ACIDS: THE (3*R*)- AND (3*S*)-FLUORO ANALOGUES OF (-)-SHIKIMIC ACID

Roger Brettle,[a] Richard Cross,[a] Martyn Frederickson,[a*1] Edwin Haslam,[a]
Fiona S. MacBeath[a] and Gareth M. Davies[b]

a. Department of Chemistry, The University of Sheffield, Sheffield, U.K., S3 7HF.
b. Zeneca Pharmaceuticals, Alderley Park, Macclesfield, Cheshire, U.K., SK10 4TG.

Abstract: (3*R*)-and (3*S*)-Fluoro-(4*R*,5*R*)-dihydroxy-1-cyclohexene-1-carboxylic acids (the (3*R*)-and (3*S*)-fluoro analogues of (-)-shikimic acid) have been synthesised from (-)-shikimic acid *via* an intermediate epoxide (a fungal metabolite from *Chalara microspora*) that underwent acid catalysed hydrolysis to afford the first stereospecific synthesis of (-)-3-*epi*-shikimic acid.

The shikimate pathway[2-4] is a biosynthetic pathway utilized by plants, fungi and micro-organisms for the synthesis of several essential aromatic metabolites including the three commonly occurring aromatic L-α-amino acids (Phe, Tyr, Trp), the folate coenzymes and various isoprenoid quinones. Compounds that inhibit the enzymes which catalyse the diverse biochemical transformations *en route* from acyclic C_3 and C_4 units to aromatics have been highlighted as potential anti-fungal, bacteriocidal or herbicidal agents following the discovery that *N*-phosphonomethylglycine (glyphosate, marketed by Monsanto as Roundup®) possesses post-emergence herbicidal properties[5] as a result of its extreme affinity for the enzyme 5-enolpyruvyl-shikimate-3-phosphate synthase (5-EPS-3-P synthase).



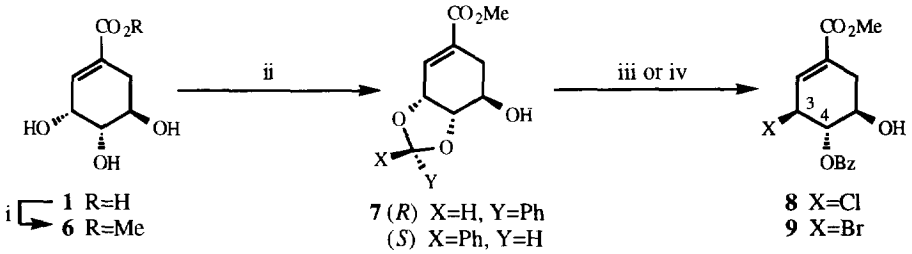
1 **2** **3** **4** **5**

We have for some time been interested in the development of synthetic routes to compounds that closely mimic shikimate pathway intermediates and have embarked upon a program of research in this area utilizing (-)-shikimic acid **1** as a precursor concentrating our efforts on the synthesis of 3-substituted shikimate derivatives. We have recently described[6] the first successful methods for the incorporation of nitrogenous functionality at C-3 of the shikimate nucleus and have highlighted the synthesis of the (3*R*)-amino shikimate derivative **2** directly from the parent acid **1**.

The syntheses of both 6α- and 6β-fluoroshikimic acids by several research groups[7-9] together with a recent report of 2-chloroshikimic acid[10] has led us to investigate methods suitable for the incorporation of a fluorine atom at C-3 of the shikimate ring as a mimic of the natural hydroxyl group (both on steric and electronic grounds) but with the distinction that, where hydrogen bonding is possible, unlike an -OH group

fluorine may act only as a hydrogen bond acceptor and not as a donor. In this communication we wish to report methods for the incorporation of fluorine, chlorine and bromine at C-3 of the shikimate ring and we describe herein the synthesis of both the 3α- and 3β-fluoro acids **3** and **4** together with the first stereospecific[11] synthesis of 3-*epi*-shikimic acid **5** directly from the natural acid **1**.

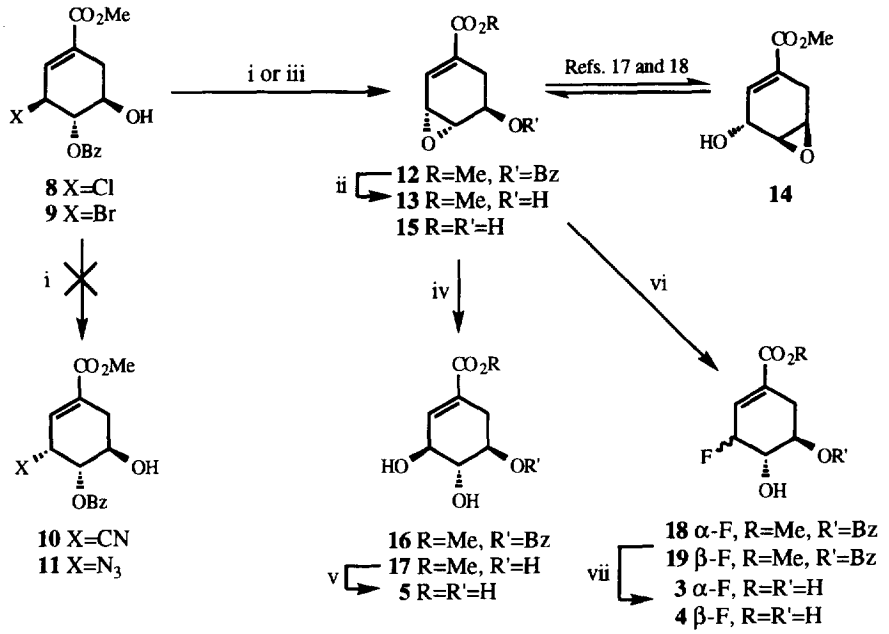
(-)-Shikimic acid **1** was isolated from the ground seeds and carpels of star aniseed[12] according to a known procedure.[13] Treatment of **1** with acidified methanol gave the known ester **6** quantitatively;[14] selective 3,4-*cis*-diol protection of **6** was effected with benzaldehyde dimethyl acetal in refluxing acidic THF to yield acetals **7** (72%, *R*:*S* 3:2).[6] Radical bromination of **7** using *N*-chlorosuccinimide (C_6H_6, Δ) or *N*-bromosuccinimide[15] (CCl_4, 20°C) afforded the 3β-chloride **8** (80%) and 3β-bromide **9** (62%) respectively; the *trans*-3,4-stereochemistry in halides **8** and **9** was clearly evident from the larger coupling constants between H-3 and H-4 ($J_{3,4}$ 7·5-8 Hz) when compared to those resulting from the 3,4-*cis*-sterochemical arrangements of **1**, **6** and **7** ($J_{3,4}$ 4-5 Hz).



Reagents and conditions: i, 1% HCl, MeOH, reflux; ii, $PhCH(OMe)_2$, $TsOH{\cdot}H_2O$, THF, reflux; iii, NCS, C_6H_6, reflux; iv, NBS, CCl_4

Attempted replacement of halide in both **8** and **9** with cyanide in warm methanol to afford nitrile **10** (in a manner analogous to that used to prepare azide **11**)[6] failed, instead rapid benzoyl migration followed by ring closure resulted in the formation of epoxide **12** (64%). Methoxide induced debenzoylation of **12** afforded the known epoxyol **13** (a fungal metabolite isolated from *Chalara microspora*);[16] alternatively, treatment of **9** with potassium carbonate in tetrahydrofuran (64°C) afforded 5-benzoate **12** and addition of methanol to the reaction mixture resulted in concomitant debenzoylation to **13** (82%). Epoxyol **13** has proven to be the subject of some controversy since the two groups[16-18] to have reported its synthesis have offered widely differing values for its specific rotation. Ganem[17,18] has suggested that a rapid base induced Payne rearrangement[19] of **13** to the 'more stable epoxyol isomer'[18] **14** may be the cause of this discrepancy; epoxyol **14** has been elegantly utilized by Berchtold in a synthesis of (-)-chorismic acid.[20]

In our hands, epoxide **13** has proven to be far less susceptible to rearrangement to **14** under basic conditions than suggested previously,[18] indeed epoxyol **13** was found to be stable under a variety of basic conditions (NaH, K_2CO_3 etc.) in various solvents (THF, MeOH etc.); formation of **14** from **13** could only be observed using methoxide ion in neat methanol at room temperature or above. Hydrolysis of **13** (NaOH, H_2O) afforded a 1:1 mixture of epoxy acid **15** and 3-*epi*-acid **5** (80%) which was smoothly converted to solely **5** upon attempted separation by reverse-phase HPLC under acidic conditions (using $MeCN:H_2O:CF_3CO_2H$ as eluent); the *trans*-3,4-stereochemistry in **5** was clearly evident from coupling constant data ($J_{3,4}$ 8 Hz).



Reagents and conditions: i, KCN, MeOH, 40°C; ii, NaOMe, MeOH, 0°C; iii, K_2CO_3, MeOH, THF, reflux; iv, CF_3CO_2H, H_2O, 20°C; v, NaOH, H_2O, 20°C; vi, 70% HF, C_5H_5N, 0°C; vii, 6M HCl, dioxane, 60-70°C

The discovery of the acid lability of epoxyol **13** allowed us to develop a new and stereospecific synthesis of (-)-3-*epi*-shikimic acid **5**. Treatment of **13** with aqueous trifluoroacetic acid afforded methyl ester **17** quantitatively which was readily saponified (NaOH, H_2O, 20°C) to yield acid **5** (81%) after ion-exchange chromatography. Both ester **17** and acid **5** have, to the best of our knowledge, only previously been prepared either in racemic form[11] or as mixtures contaminated with their C-3 epimers from which the desired compounds were isolated by fractional crystallization;[11,21] our approach thus allows the first *stereospecific* synthesis of both laevorotatory ester **17** and acid **5** on a preparative scale.

A similar protocol using polyhydrogen fluoride/pyridine complex has allowed the synthesis of the (3*R*)- and (3*S*)-fluoro acids **3** and **4**. Treatment of 5-benzoate **12** with an excess of Olah's reagent[22] at 0°C resulted in the regiospecific opening of the epoxide ring to afford a mixture of the 3β-alcohol **16** (17%; $J_{3,4}$ 7·5 Hz), together with both the 3α-fluoride **18** (8%) and 3β-fluoride **19** (48%, $J_{3,4}$ 8 Hz). Careful analysis of a mixture of **18** and **19** using a combination of ^1H, ^{13}C and ^{19}F nmr spectroscopy showed clearly that fluoride ion had been incorporated at C-3 of the ring; no regioisomeric 4-fluorinated products or 1-fluorinated products (resulting from oxirane cleavage *via* an alternative S_N2' mechanism) could be detected. Acid induced hydrolysis of **18** and **19** in acidic aqueous dioxane afforded a mixture of the 3α- and 3β-fluoro acids **3** (5%) and **4** (91%) from which pure 3β-fluoro acid **4** could be isolated by HPLC; notably **4** has an identical melting point to the parent acid **1** (183-186°C).

Acknowledgements: We thank the SERC, Zeneca Pharmaceuticals and The University of Sheffield for support.

REFERENCES AND NOTES

1. *Present address:* School of Chemistry, The University of Leeds, Leeds, U.K., LS2 9JT. FAX: +44 (0) 113 2336565.
2. Haslam, E. *Shikimic acid: Metabolism and Metabolites*, John Wiley and Sons, Chichester, 1993.
3. Weiss, U.; Edwards, J.M. *The Biosynthesis of Aromatic Compounds*, John Wiley and Sons, New York, 1981.
4. Campbell, M.M.; Sainsbury, M.; Searle, P.A. *Synthesis*, **1993**, 179-193.
5. Grossbard, E.; Atkinson, D. *The Herbicide Glyphosate*; Butterworths: Boston, 1985.
6. Brettle, R.; Cross, R.; Frederickson, M.; Haslam, E.; Davies, G.M. *Bioorg. Med. Chem. Lett.*, **1996**, *6*, 291-294.
7. Sutherland, J.K.; Watkins, W.J.; Bailey, J.P.; Chapman, A.K.; Davies, G.M. *J. Chem. Soc., Chem. Commun.*, **1989**, 1386-1387.
8. Bowles, S.A.; Campbell, M.M.; Sainsbury, M.; Davies, G.M. *Tetrahedron*, **1990**, *46*, 3981-3992.
9. Duggan, P.J.; Parker, E.; Coggins, J.; Abell, C. *Bioorg. Med. Chem. Lett.*, **1995**, *5*, 2347-2352.
10. Rich, R.H.; Lawrence, B.M.; Bartlett, P.A. *J. Org. Chem.*, **1994**, *59*, 693-694.
11. For a non-stereoselective synthesis of both (±)-shikimic acid and (±)-3-*epi*-shikimic acid see: Grewe, R.; Hinrichs, I. *Chem. Ber.*, **1964**, *97*, 443-448.
12. Whole star aniseed was obtained from Brome and Schimmer Ltd., Romsey Industrial Estate, Romsey, Hamphire, U.K., SO51 0HR.
13. Grewe, R.; Lorenzen, W. *Chem. Ber.*, **1953**, *86*, 928-938.
14. Grewe, R.; Jensen, H.; Schnoor, M. *Chem. Ber.*, **1956**, *89*, 898-905.
15. The quality of *N*-bromosuccinimide proved crucial to the success of this procedure; traces of bromine and hydrogen bromide impurities commonly found in commercial NBS were found to be detrimental to the course of this reaction. For optimal results the commercial material was recrystallized from hot water as large colourless plates and was dried over phosphorus pentoxide *in vacuo* prior to use.
16. Fex, T.; Trofast, J.; Wickberg, B. *Acta Chem. Scand., Ser. B*, **1981**, *35*, 91-95.
17. Wood, H.B.; Ganem, B. *Tetrahedron Lett.*, **1989**, *30*, 6257-6258.
18. Wood, H.B.; Ganem, B. *J. Am. Chem. Soc.*, **1990**, *112*, 8907-8909.
19. Payne, G.B. *J. Org. Chem.*, **1962**, *27*, 3819-3822.
20. Pawlak, J.L.; Berchtold, G.A. *J. Org. Chem.*, **1987**, *52*, 1765-1771.
21. Grewe, R.; Jeschke, J.-P. *Chem. Ber.*, **1956**, *89*, 2080-2088.
22. Olah, G.A.; Welch, J.T.; Vankar, Y.D.; Nojima, M.; Kerekes, I.; Olah, J.A. *J. Org. Chem.*, **1979**, *44*, 3872-3881.

(*Received in Belgium* 14 *February* 1996; *accepted* 6 *May* 1996)