Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 3429–3432
Tetrahedron Letters

The synthesis of 6,6-difluoroshikimic acid

Jane L. Humphreys, David J. Lowes, Karen A. Wesson and Roger C. Whitehead*

Department of Chemistry, The University of Manchester, Oxford Road, Manchester M13 9PL, UK

Received 23 February 2004; revised 25 February 2004; accepted 3 March 2004

Abstract—The synthesis of 6,6-difluoroshikimic acid (**4**) has been achieved in nine steps from the enantiopure diol **9**, which is derived from microbial dihydroxylation of iodobenzene. The synthetic strategy has also been demonstrated to be applicable to the preparation of other 6-substituted analogues of shikimic acid.

1. Introduction

The fluorinated analogues **2** and **3** of (−)-shikimic acid (**1**) (Fig. 1) have attracted a great deal of scientific interest.[1–3] Both compounds display in vitro antibacterial activity against a range of *E. coli* strains with (6*S*)-6-fluoroshikimic acid (**2**) being the more potent agent (MIC against *E. coli* K-12 of 0.1 μg/mL compared with 64 μg/mL for (6*R*)-6-fluoroshikimic acid (**3**)).[4] Both fluorinated analogues are substrates for the shikimate transport system of *E. coli*[5] and importantly, the (6*S*)-isomer **2** has been shown to be protective against a range of bacterial intraperitoneal challenges in mice.[4] Following the discovery that the shikimic acid pathway is vital for the survival of parasites of the phylum Apicomplexa,[6,7] it has recently been disclosed that both **2** and **3** inhibit the growth of the malaria parasite, *P. falciparum*.[8] Interestingly, in contrast to the situation in *E. coli*, the (6*R*)-compound **3** was reported to be significantly more potent than the (6*S*)-isomer **2** in this assay.

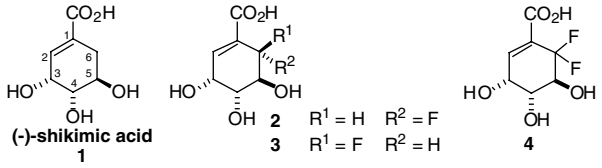


Figure 1.

The exciting discovery that **2** and **3** possess antiparasitic properties has stimulated renewed interest in the design and synthesis of novel inhibitors of enzymes on the shikimate pathway. In this Letter, we report the synthesis of compound **4**, the final member of the series of 6-fluoroshikimic acids, using an approach, which we have also demonstrated to be amenable to the preparation of other 6-substituted analogues of shikimic acid.

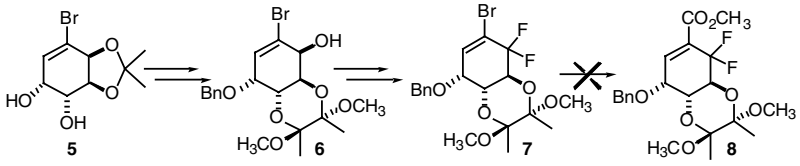
2. Results and discussion

Recently, we described the synthesis of vinyl bromide **6** in four steps from diol **5** (Scheme 1).[9]

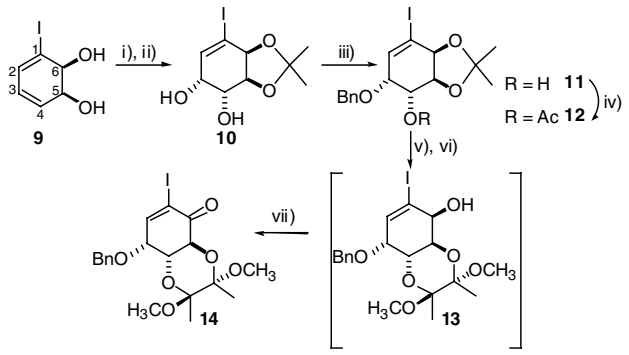
Oxidation of the allylic hydroxyl in **6** gave the expected enone which, on treatment with the nucleophilic fluorinating agent [bis-(2-methoxyethyl)]-aminosulfurtrifluoride (DeoxoFluor®)[10] was converted to the *gem*-difluoride **7**. Unfortunately, all attempts to introduce a carboxyl substituent at C1 of **7** using Pd(0) chemistry, as well as using other *trans*-metallation protocols, met with failure.[9] It is well documented that aryl and vinyl bromides are less reactive in Pd(0) catalysed C–C bond forming reactions than the corresponding iodides and we decided, therefore, to turn our attention to the preparation of the analogue of **7** bearing an iodine atom at C1. We thus embarked on the synthesis of 6,6-difluoroshikimic acid using the enantiopure iodo-diol **9** as starting material (Scheme 2).[11] Following the general procedure of Hudlicky,[12] protection of the vicinal diol of **9** as its acetonide followed by face-selective *cis*-dihydroxylation of the 3,4-double bond gave diol **10**. Selective protection of the allylic hydroxyl of **10** as its benzyl ether was accomplished in excellent yield via an intermediate

* Corresponding author. Tel.: +44-161-275-7856; fax: +44-161-275-4939; e-mail: roger.whitehead@man.ac.uk

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.03.033



Scheme 1.



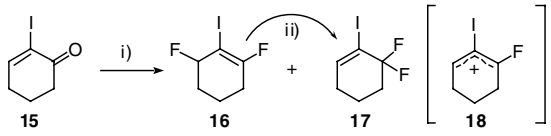
Scheme 2. Reagents and conditions: (i) $(CH_3O)_2C(CH_3)_2$, *p*TSA, CH_2Cl_2; (ii) OsO_4 (cat.), NMO, ^tBuOH, H_2O, 94% over two steps; (iii) Bu_2SnO, $C_6H_5CH_3$, CH_3OH, Δ then BnBr, Bu_4NI, $C_6H_5CH_3$, 130 °C, 91%; (iv) Ac_2O, DMAP, py, CH_2Cl_2; (v) TFA/H_2O (6:1), rt; (vi) butan-2,3-dione, $(CH_3O)_3CH$, CSA, CH_3OH, Δ; (vii) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C to rt, 36% over three steps.

stannylene acetal.[13,14] The regioselectivity of this reaction was confirmed by acetylation of the remaining free hydroxyl of **11** to give **12**: comparison of the ^1H NMR spectra of the two compounds confirmed a significant downfield shift of the resonance assigned to C(4)*H* in compound **12** (δ_H: ~4.41 for **11**, 5.53 for **12**). *trans*-Ketalisation of **11** using the conditions of Ley et al.[15] gave an inseparable mixture of butane diacetals, which was oxidised using Swern conditions[16] to give **14** in a disappointing yield (~15%) over two steps from **11**. A lengthier three-step procedure was thus developed, involving initial hydrolysis of **11** to give the corresponding triol, followed by ketalisation to give an inseparable mixture of diacetals **13** and then oxidation to provide the desired enone **14** in an acceptable overall yield of 36%.

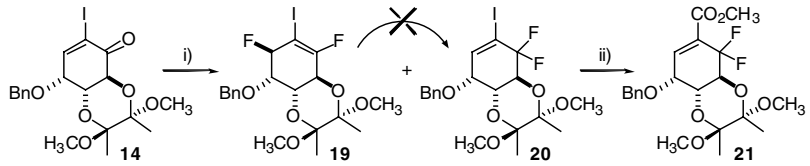
With enone **14** in hand, we were able to investigate the key fluorodeoxygenation step necessary for introduction of geminal fluorines at C6. Previous work in our research group[17] had indicated that fluorodeoxygenation of model compound **15** under standard conditions, was not only low-yielding but also gave approximately equimolar amounts of the desired compound **17** and an isomer **16** (Scheme 3). Pleasingly, in the model system, it was possible to develop mild conditions, which allowed efficient isomerisation of **16**, via the presumed intermediacy of a transient allylic carbenium ion **18**, to give **17**.

Fluorodeoxygenation of α-iodo enone **14** proceeded smoothly to give an approximately 1:1 mixture of difluorides **19** and **20** from which the desired *gem*-difluoride **20** could be isolated in adequate yield (Scheme 4). Unfortunately, we were unable to discover conditions under which vinyl fluoride **19** could be isomerised to *gem*-difluoride **20**, presumably reflecting the instability of the highly oxygenated allylic carbenium ion, which is a necessary intermediate in this interconversion. We were pleased, however, to find that Pd(0) mediated carbonylation of **20** proceeded smoothly and in reasonable yield to give the conjugated ester **21**.[18]

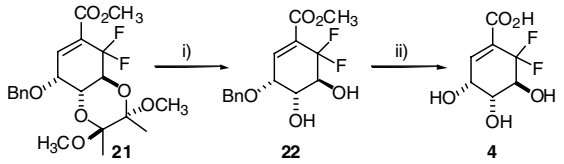
With compound **21** in hand, all that remained to be accomplished was complete deprotection to give the target material. Several plausible routes were considered with the main requirement being for conditions that would allow efficient removal of the benzyl protecting group without recourse to hydrogenolysis procedures and that were mild enough to avoid competitive, destructive aromatisation processes. Ultimately, the preparation of **4** was achieved in two steps (Scheme 5). Firstly, the butane diacetal (BDA) group was removed in quantitative fashion by stirring **21** in a mixture of TFA and water (6:1) at room temperature. Secondly, and somewhat surprisingly, removal of the benzyl protecting group and concomitant ester hydrolysis was accomplished by heating a solution of the diol **22** in



Scheme 3. Reagents and conditions: (i) Morph-DAST, C_6H_6, 80 °C, 24 h, 26% combined yield of **16** and **17**; (ii) 4 Å mol sieves, CH_2Cl_2, rt, 8 h, quant.



Scheme 4. Reagents and conditions: (i) DeoxoFluor®, rt, 72 h, 30% of **19**, 36% of **20**; (ii) $Pd(OAc)_2$, diisopropylethylamine, tri-2-furylphosphine, CH_3OH, CO, DMF, rt, 24 h, 56%.



Scheme 5. Reagents and conditions: (i) TFA/H_2O (6:1), rt, 3 h; (ii) concd HCl/H_2O (1:1), 60–70 °C, 12 h then HPLC, 68% over two steps.

~6 M HCl at 60–70 °C for 12 h.[19a,b,c] Analysis by ^1H NMR of the crude product from this sequence indicated that no aromatisation had occurred and the target compound **4** was generated in essentially pure form.[20]

A long-term goal of our research endeavours has been the development of a 'divergent' synthetic strategy, which will allow the preparation of a variety of 6-substituted analogues of shikimic acid. In this regard we envisaged the allylic alcohol **13** to be a pivotal intermediate, however, preparation of a pure sample of this compound had not been possible from the acetonide **11** (vide supra). We therefore turned our attention to the 'aromatic Finkelstein reaction' recently developed by Buchwald and co-workers, which allows the conversion of aryl bromides to the corresponding aryl iodides by the action of a catalytic quantity of CuI, KI and a diamine additive.[21] In the original publication, one example of a high-yielding halogen exchange of a vinyl bromide was reported. Encouraged by this, we initiated an investigation into the halogen exchange of vinyl bromide **6** with a view to preparing a sample of the vinyl iodide **13**. Pleasingly, reaction of **6** under the conditions described by Buchwald, resulted in quite clean conversion to the vinyl iodide **13**, which was isolated in 72% yield after purification by flash chromatography (Scheme 6). Fluorodeoxygenation of **13** using the nucleophilic fluorinating agent DAST (Et_2NSF_3)[22a,b] proceeded with inversion of configuration to give the allylic fluoride **23** and subsequent Pd(0) mediated carbonylation occurred reasonably smoothly to give the conjugated ester **24**.[23] The successful outcome of this short synthetic sequence demonstrates the potential versatility of the vinyl iodide **13** as a useful precursor for the synthesis of other shikimic acid analogues.

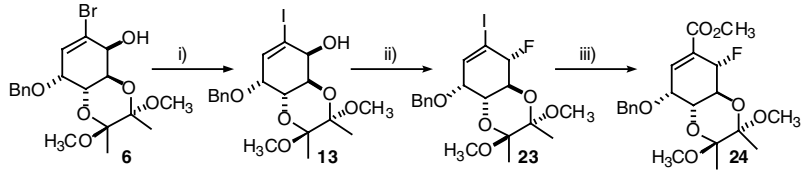
In summary, we have prepared the novel analogue **4** of (−)-shikimic acid in nine steps from the enantiopure diol **9**. The allylic alcohol **13**, although not directly accessible in pure form from **9**, has been synthesised via application of Buchwald's 'aromatic Finkelstein reaction'.[21] The potential utility of **13** as a diversification point for the synthesis of other analogues of (−)-shikimic acid has been demonstrated by the preparation of a differentially protected synthetic precursor to the known antimicrobial agent (6*S*)-6-fluoroshikimic acid (**2**).

Acknowledgements

We acknowledge, with thanks, the EPSRC for funding (J.L.H, D.J.L and K.A.W.) and we wish to acknowledge the EPSRC National Mass Spectrometry Service Centre in Swansea for the provision of high resolution mass measurements. We are particularly grateful to Professor Derek Boyd of the Queens University in Belfast for the generous donation of diol **9** and also to Rehana Sung for assistance with HPLC purification of compound **4**.

References and notes

1. Sutherland, J. K.; Watkins, W. J.; Bailey, J. P.; Chapman, A. K.; Davies, G. M. *J. Chem. Soc., Chem. Commun.* **1989**, 1386–1387.
2. Duggan, P. J.; Parker, E.; Coggins, J.; Abell, C. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2347–2352.
3. Song, C.; Jiang, S.; Singh, G. *Tetrahedron Lett.* **2001**, *42*, 9069–9071.
4. Davies, G. M.; Barrett-Bee, K. J.; Jude, D. A.; Lehan, M.; Nichols, W. W.; Pinder, P. E.; Thain, J. L.; Watkins, W. J.; Wilson, R. G. *Antimicrob. Agents Chemother.* **1994**, *38*, 403–406.
5. Jude, D. A.; Ewart, C. D. C.; Thain, J. L.; Davies, G. M.; Nichols, W. W. *Biochim. Biophys. Acta* **1996**, *1279*, 125–129.
6. Roberts, F.; Roberts, C. W.; Johnson, J. J.; Kyle, D. E.; Krell, T.; Coggins, J. R.; Coombs, G. H.; Millous, W. K.; Tzipori, S.; Fergusson, D. J. P.; Chakrabarti, D.; McLeod, R. *Nature* **1998**, 801–805.
7. Roberts, C. W.; Roberts, F.; Lyons, R. E.; Kirisits, M. J.; Mui, E. J.; Finnerty, J.; Johnson, J. J.; Ferguson, D. J. P.; Coggins, J. R.; Krell, T.; Coombs, G. H.; Milhous, W. K.; Kyle, D. E.; Tzipori, S.; Barnwell, J.; Dame, J. B.; Carlton, J.; McLeod, R. *J. Infectious Diseases* **2002**, *185*, S25–S36.
8. McConkey, G. A. *Antimicrob. Agents Chemother.* **1999**, *43*, 175–177.
9. Begum, L.; Box, J. M.; Drew, M. G. B.; Harwood, L. M.; Humphreys, J. L.; Lowes, D. J.; Morris, G. A.; Redon, P. M.; Walker, F. M.; Whitehead, R. C. *Tetrahedron* **2003**, *59*, 4827–4841.
10. Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M.; Cheng, H. *J. Org. Chem.* **1999**, *64*, 7048–7054.
11. The diol **9** was generously donated by Professor Derek Boyd at The Queens University of Belfast. It is commercially available from the QUESTOR Centre at the Queens University of Belfast. For further details, contact Profes-



Scheme 6. Reagents and conditions: (i) CuI, KI, *N*,*N*′-dimethylethylenediamine, ^{n}BuOH, Δ, 72%; (ii) Et_2NSF_3, CH_2Cl_2, 0 °C to rt, 53% (iii) $Pd(OAc)_2$, diisopropylethylamine, tri-2-furylphosphine, CH_3OH, CO, DMF, rt, 24 h, 58%.

sor Derek Boyd, The School of Chemistry, The Queens University of Belfast, David Keir Building, Stranmills Road, Belfast BT9 5AG, Northern Ireland.
12. Hudlicky, T.; Price, J. D.; Rulin, F.; Tsunoda, T. *J. Am. Chem. Soc.* **1990**, *112*, 9439–9440.
13. Simas, A. B. C.; Pais, K. C.; da Silva, A. A. T. *J. Org. Chem.* **2003**, *68*, 5426–5428.
14. For a review see: David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643–663.
15. For a review see: Ley, S. V.; Baeschlin, D. K.; Dixon, D. J.; Foster, A. C.; Owen, D. R.; Ince, S. J.; Priepke, H. W. M.; Reynolds, D. J. *Chem. Rev.* **2001**, *101*, 53–80.
16. Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185.
17. Box, J. M.; Harwood, L. M.; Whitehead, R. C. *Synlett* **1997**, 571–573.
18. Spectroscopic data for compound **21**. Mp 131–133 °C; $[\alpha]_D^{19}$ +2.9 (*c* 1.36, CH_2Cl_2); ν_{max} (film)/cm^{-1} 1733s (C=O); δ_H (400 MHz; $CDCl_3$) 1.39 and 1.43 (2×3H, 2×s, 2×butyl CH_3), 3.30 and 3.36 (2×3H, 2×s, 2×acetal OCH_3), 3.82 (3H, s, CO_2CH_3), 3.96 (1H, dd, *J* 10.8, 3.8, C(4)*H*), 4.25 (1H, dd, *J* 5.8, 3.8, C(3)*H*), 4.50 (1H, dt, *J* 13.6, 10.8, C(5)*H*), 4.68 (1H, d, *J* 11.2, one of benzyl CH_2), 5.05 (1H, d, *J* 11.2, one of benzyl CH_2), 7.08 (1H, dd, *J* 5.8, 2.4, C(2)*H*), 7.29–7.40 (3H, m, aromatic *m*- and *p*-C*H*), 7.45 (2H, d, *J* 7.6, aromatic *o*-C*H*); δ_C (75 MHz; $CDCl_3$) 17.90 and 17.96 (2×butyl *C*H_3), 48.45 and 48.47 (2×acetal O*C*H_3), 52.76 (CO_2CH_3), 66.87 (dd, *J* 21.3, 18.4, *C*(5)H), 67.10 (dd, *J* 6.0, 1.2, *C*(4)H), 70.06 (*C*(3)H), 74.81 (benzyl *C*H_2), 99.57 and 99.81 (2×acetal *C*), 115.95 (t, *J* 245.1, *C*(6)F_2), 128.28, 128.59 and 128.72 (aromatic *C*H), 129.1 (dd, *J* 26.5, 22.9, *C*(1)), 138.38 (aromatic *ipso*-*C*), 141.3 (t, *J* 6.6, *C*(2)H), 163.23 (t, *J* 1.4, *C*=O); δ_F (376 MHz; $CDCl_3$) −106.45 (1F, ddd, *J* 278.3, 10.8, 2.4, one of C(6)F_2), −107.40 (1F, dd, *J* 278.3, 13.6, one of C(6)F_2); *m*/*z* (CI/NH_3) 446 (MNH_4^+, 100%), 414 (25), 340 (52), 188 (25), 102 (67); (found 446.1987, $C_{21}H_{30}F_2NO_7$ (MNH_4^+) requires 446.1990).
19. (a) For some examples of acid mediated removal of benzyl protecting groups, see: Baker, W.; Brown, N. C. *J. Chem. Soc.* **1948**, 2303–2307; (b) Kametani, T.; Yagi, H.; Satoh, F.; Fukumoto, K. *J. Chem. Soc.* **1968**, 271–275; (c) Marsh, J. P.; Goodman, L. *J. Org. Chem.* **1965**, *30*, 2491–2492.
20. Spectroscopic data for compound **4**. $[\alpha]_D^{25}$ −128.0 (*c* 0.10, H_2O); δ_H (400 MHz; D_2O) 3.78 (1H, ddd, *J* 9.6, 4.0, 1.6, C(4)*H*), 3.99 (1H, ~dt, *J* 12.2, 9.6, C(5)*H*), 4.38 (1H, br t, *J* 4.0, C(3)*H*), 6.91 (1H, dd, *J* 4.4, 2.0, C(2)*H*); δ_F (282.1 MHz; D_2O) −104.48 (1F, br d, *J* 276.9, one of C(6)F_2), −109.24 (1F, dd, *J* 276.9, 12.2, one of C(6)F_2); *m*/*z* (negative ion electrospray) 209 (60%, $[M-H]^-$), 189 (100); (found 209.0270, $C_7H_7F_2O_5$ ($[M-H]^-$) requires 209.0267).
21. Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14844–14845.
22. (a) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574–578; (b) Hudlicky, M. *Org. React. (NY)* **1988**, *35*, 513–637.
23. Spectroscopic data for compound **24**. Mp 113–115 °C; $[\alpha]_D^{19}$ +34.5 (*c* 1.08, $CHCl_3$); ν_{max} (film)/cm^{-1} 1730s (C=O); δ_H (300 MHz; $CDCl_3$) 1.47 and 1.49 (2×3H, 2×s, 2×butyl CH_3), 3.38 and 3.47 (2×3H, 2×s, 2×acetal OCH_3), 3.69 (1H, dd, *J* 11.4, 3.4, C(4)*H*), 3.89 (3H, s, CO_2CH_3), 4.20 (1H, dd, *J* 6.0, 3.4, C(3)*H*), 4.57 (1H, ddd, *J* 21.3, 11.4, 7.1, C(5)*H*), 4.73 (1H, d, *J* 11.4, one of benzyl CH_2), 5.05 (1H, d, *J* 11.4, one of benzyl CH_2), 5.38 (1H, dd, *J* 49.2, 7.1, C(6)*H*), 6.91 (1H, d, *J* 6.0, C(2)*H*), 7.34–7.51 (5H, m, aromatic C*H*); δ_C (75 MHz; $CDCl_3$) 17.95 and 17.99 (2×butyl *C*H_3), 48.30 and 48.36 (2×acetal O*C*H_3), 52.52 (CO_2CH_3), 68.12 (d, *J* 4.6, *C*(4)H), 68.32 (d, *J* 8.1, *C*(5)H), 70.61 (*C*(3)H), 74.10 (benzyl *C*H_2), 88.65 (d, *J* 175.7, *C*(6)FH), 99.21 and 99.66 (2×acetal *C*), 128.06, 128.47 and 128.63 (aromatic *C*H), 131.95 (d, *J* 19.2, *C*(1)), 137.26 (d, *J* 5.4, *C*(2)H), 138.71 (aromatic *ipso*-*C*), 165.30 (*C*=O); δ_F (376 MHz; $CDCl_3$) −183.86 (dd, *J* 49.2, 21.3, C(6)H*F*); *m*/*z* (positive ion electrospray) 433 (100%, $[M + Na]^+$).