Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 6249–6253
Tetrahedron Letters

Approaches to the synthesis of 3-fluoroshikimic acids

Lovely Begum,[a] Michael G. B. Drew,[a] Jane L. Humphreys,[b] David J. Lowes,[b] Pamela R. Russi,[b] Helen L. Whitby[b] and Roger C. Whitehead[b,*]

[a]*Department of Chemistry, The University of Reading, Whiteknights, Reading RG6 6AD, UK*
[b]*Department of Chemistry, The University of Manchester, Oxford Road, Manchester M13 9PL, UK*

Received 28 May 2004; revised 16 June 2004; accepted 22 June 2004

Abstract—Exploitation of the dual dehydrating and fluorodeoxygenating properties of the dialkylaminosulfurtrifluorides has allowed access to the C3-fluorinated analogues of (−)-shikimic acid.

1. Introduction

Over recent years, there has been much interest in the efficient preparation of analogues of (−)-shikimic acid (**1**), which have been targeted as likely inhibitors of enzymes on the shikimic acid pathway and which are of relevance as potential antifungal, antibacterial and antiparasitic agents. A principal goal of our present research is the synthesis of analogues of (−)-shikimic acid (**1**), which either inhibit shikimate kinase, or alternatively undergo intracellular phosphorylation by the kinase and thereby act as prodrugs for inhibitors of enzymes further downstream on the pathway (e.g., EPSP synthase or chorismate synthase (Scheme 1)).[1a,b]

As part of a research program concerned with the synthesis and biological evaluation of fluorinated analogues of polyoxygenated enzyme substrates, we became interested in the 3-deoxy-3-fluorinated analogues (**5**, **6** and **7**) of (−)-shikimic acid (Fig. 1). Our principal goal was the development of a short synthesis of the (3*R*)-3-fluoro-

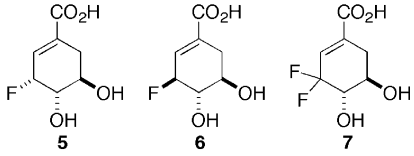
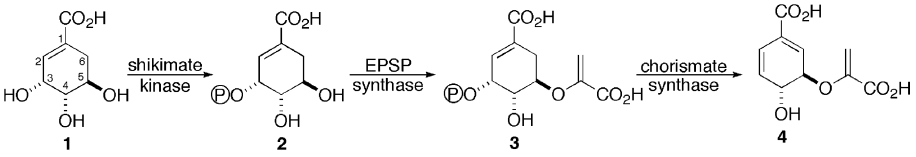


Figure 1.

isomer **5**, a compound, which was previously reported by Haslam and collaborators as a very minor product isolated during the synthesis of the diastereoisomeric compound **6**.[2a,b] Compound **5** was of interest to us with regard to its potential antimicrobial properties, and also as a likely competitive inhibitor of shikimate kinase, which might assist in the crystallographic location of the shikimate binding site. We report herein, novel synthetic approaches to compounds **5** and **6** and a modification of the literature synthesis of the difluorinated analogue **7**.[3]



Scheme 1.

* 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.2004.06.092

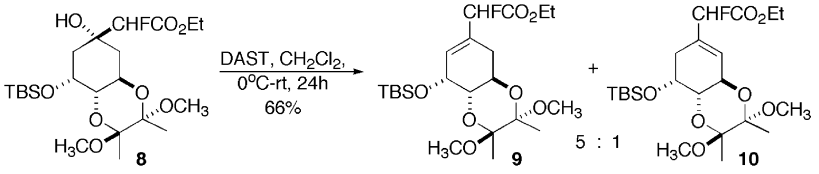
2. Results and discussion

Over recent years we, and others, have carried out extensive investigations into the application of aminosulfurtrifluorides as versatile reagents for the fluorodeoxygenation of organic substrates. Of particular relevance to our current research are the literature reports, which describe regioselective reactions with substrates possessing several unprotected hydroxyl groups.[4a,b] A less extensively exploited property of aminosulfurtrifluorides is their ability to mediate mild and efficient dehydration reactions on tertiary substrates.[5] A pertinent example from this laboratory is the dehydration of compound **8**, which occurred at ambient temperature and with a pleasing level of regiocontrol (Scheme 2).

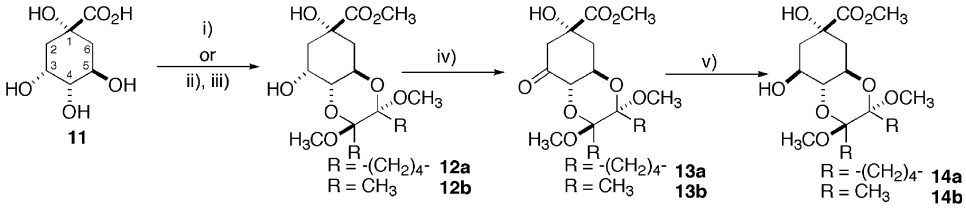
In designing a synthesis of compound **5**, it was our intention to marry the fluorodeoxygenating and dehydrating properties of the aminosulfurtrifluorides. With this aim in mind, we envisaged the diacetal protected 3-*epi*-quinates **14a**,**b** to be key intermediates (Scheme 3). We reasoned that these compounds may undergo double activation in the presence of an excess of aminosulfurtrifluoride, followed by tandem regioselective dehydration and fluorodeoxygenation at C3 to give the desired (3*R*)-3-fluoro-shikimates.

The diacetal protected methyl quinates **12a**,**b** were prepared from (−)-quinic acid (**11**) using standard procedures (Scheme 3).[6] Although much of the chemistry reported herein has been carried out on both series of compounds, the superior yield of preparation of the butane diacetal (BDA) protected compound **12b** makes this our protecting group of choice. Oxidation of the free secondary hydroxyl in **12b** was accomplished cleanly using the Ley–Griffith reagent (tetrapropylammonium perruthenate):[7] use of this reagent avoided any erosion in yield due to competitive elimination processes, which have been reported to occur during oxidation of **12b** under Swern conditions.[3,8] Directed reduction of the ketone **13b** was then accomplished in good yield using sodium triacetoxyborohydride to give the protected 3-*epi*-quinate **14b**.[9a,b] With **14b** in hand, we were in position to investigate the tandem dehydration–fluorodeoxygenation sequence. Thus, addition of a dichloromethane solution of **14b** to an ice-cooled solution of diethylaminosulfurtrifluoride (DAST, 2.2 equiv) in dichloromethane resulted in the formation of a principle fluorine-containing compound, which was isolated, after chromatography, in 27% yield (Scheme 4). NMR analysis of this material indicated it to be the desired (3*R*)-3-fluoro isomer **15b**.[10,11]

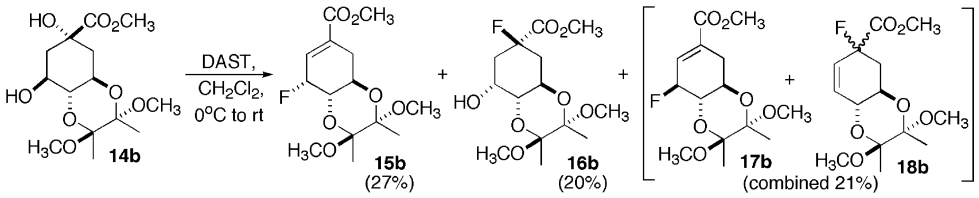
The tertiary fluoride **16b**, in which the stereochemistry at both C1 and C3 had been inverted, was also isolated from this reaction in 20% yield.[12] An inseparable mixture (~1:1) of (3*S*)-3-fluoro compound **17b** and the allylic fluoride **18b** was obtained in 21% combined yield. A similar product distribution was obtained when the reaction was carried out with [bis-(2-methoxyethyl)]-amino-



Scheme 2.



Scheme 3. Reagents and conditions: (i) CH_3OH, Amberlite® IR 120(H), Δ, 8 h; (ii) 1,1,2,2-tetramethoxycyclohexane, $(CH_3O)_3CH$, camphorsulfonic acid, CH_3OH, Δ, 12 h, 73% yield of **12a** over two steps; (iii) butan-2,3-dione, $(CH_3O)_3CH$, camphorsulfonic acid, CH_3OH, Δ, 12 h, 98% yield of **12b** over one step; (iv) tetrapropylammoniumperruthenate, *N*-methylmorpholine-*N*-oxide, 4 Å molecular sieves, CH_2Cl_2, rt, 5 h, 88% yield for **13a**, 93% yield for **13b**; (v) $NaBH(OAc)_3$, THF, 0 °C to rt, 74% for **14a**, 82% for **14b**.



Scheme 4.

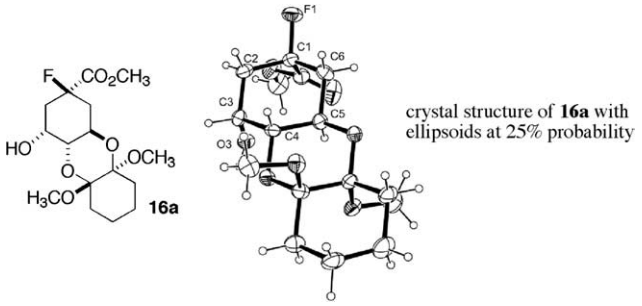


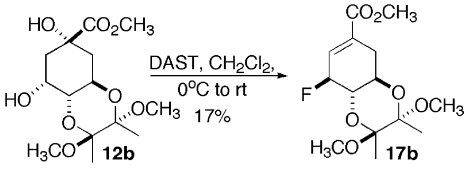
Figure 2.

sulfurtrifluoride (DeoxoFluor®).[13] Confirmation of the stereochemical assignment of the tertiary fluoride **16b** was accomplished by X-ray crystallographic analysis of the corresponding cyclohexanediacetal (CDA) protected material **16a** (Fig. 2).[14,15]

Disappointingly, similar reaction of diacetal protected quinate **12b** was less efficient and resulted in generation of a mixture of compounds from which (3*S*)-3-fluoro isomer **17b** was isolated in 17% yield (Scheme 5).[16]

Alternative syntheses of **15b** and **17b** have also been developed, which involve additional protection and deprotection steps and are consequently lengthier than the routes described above (Scheme 6).

Thus, monosilylation of **12b** followed by regioselective dehydration, according to the procedure recently reported by ourselves,[1a,5] furnished protected methyl shikimate **19** in excellent yield. Deblocking of the C3 oxygen substituent proceeded cleanly to give the allylic alcohol **20**, which underwent smooth fluorodeoxygenation to give the (3*S*)-3-fluoro isomer **17b**. Mitsunobu inversion of **20**[17] followed by methanolysis of the resulting benzoate ester gave (3*S*)-allylic alcohol **21**,[8,18,19] which underwent fluorodeoxygenation to give the (3*R*)-3-fluoro isomer **15b** as the major product (19% overall yield from **12b**). This last reaction was less efficient than the corresponding transformation of **20**, with significant quantities of the (3*S*)-3-fluoro isomer **17b** and tertiary allylic fluoride **18b** also being generated. This finding is presumed to be a consequence of the pseudo-equatorial orientation of the C3 substituent in **21**, which may retard direct S_N2 displacement by fluoride.

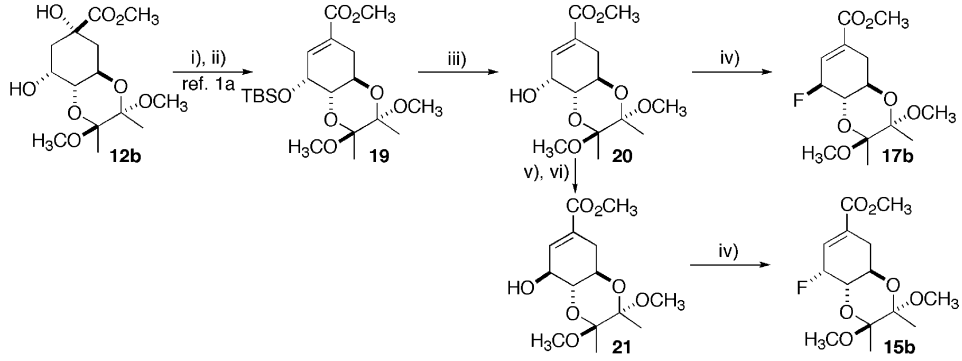


Scheme 5.

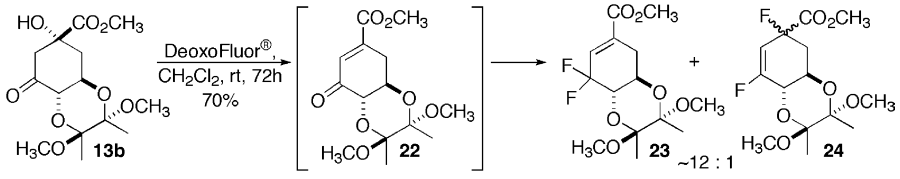
In order to complete the syntheses of all C3-fluorinated analogues of shikimic acid, we have again exploited the dual dehydrating and fluorodeoxygenating properties of the aminosulfurtrifluorides in a modification of the literature synthesis of the difluorinated analogue **7**.[3] Thus, treatment of hydroxyketone **13b** with 5 equiv of DeoxoFluor®[13] in dichloromethane for a prolonged reaction time resulted in dehydration, to give enone **22**, and sequential fluorodeoxygenation to give the *gem*-difluoride **23**. The product from the reaction was invariably contaminated with trace amounts of an inseparable impurity believed to be a mixture of the diastereoisomeric vinyl fluorides **24**, which may arise from allylic rearrangement during the fluorodeoxygenation step [δ_F (376.3 MHz; $CDCl_3$) (major impurity) −109.9 (1F, m) and −131.2 (1F, m)]. It is noteworthy that, in our hands, all attempts to prepare **23**, either from ketone **13b** or from enone **22**, have resulted in generation of this inseparable impurity: the level of contamination varying in an unpredictable fashion with the nature of the reaction conditions[20] (Scheme 7).

Two-step deprotection of the three fluorinated compounds **15b**, **17b** and **23** furnished the target compounds **5**, **6** and **7**, which were each purified by reverse phase HPLC.[21] In the case of deprotection of **23**, the unwanted contaminant derived from **24** was removed by chromatography after the initial saponification step (Scheme 8).

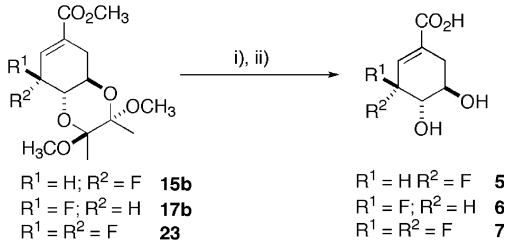
In summary, we have successfully prepared all three C3-fluorinated analogues of (−)-shikimic acid (**5**, **6** and **7**) from commercially available (−)-quinic acid (**11**). The



Scheme 6. Reagents and conditions: (i) *tert*-butyldimethylsilyl trifluoromethanesulfonate, Et_3N, CH_2Cl_2, 0 °C, 2 h, 97%; (ii) $Ph_2S[OC(CF_3)_2Ph]_2$, CH_2Cl_2, rt, 24 h, 84%; (iii) TBAF, THF, 0 °C to rt, 3 h, 91%; (iv) Et_2NSF_3, CH_2Cl_2, 0 °C to rt, 17 h, 72% for **17b**, 41% for **15b**; (v) Ph_3P, diisopropylazodicarboxylate, $C_6H_5CO_2H$, THF, rt, 4 h, 90%; (vi) K_2CO_3, CH_3OH, rt, 3 h, 71%.



Scheme 7.



Scheme 8. Reagents and conditions: (i) LiOH, H_2O, CH_3OH, rt; (ii) TFA–H_2O (6:1), rt, 78% for **5**, 54% for **6**, 63% for **7**.

most expedient syntheses of **5**, **6** and **7** utilised the dual dehydrating *and* fluorodeoxygenating properties of the aminosulfurtrifluorides and were accomplished in six, four and five steps, respectively. In the case of (3*S*)-3-fluoroshikimic acid (**6**) a lengthier seven step synthesis was found to be higher yielding overall but this was not the case for the isomeric compound **5**.

Acknowledgements

We acknowledge, with thanks, the EPSRC for funding (L.B., J.L.H, D.J.L and H.L.W.) and we wish to acknowledge the EPSRC National Mass Spectrometry Service Centre in Swansea for the provision of high resolution mass measurements. We thank the EPSRC and the University of Reading for funds for the Image Plate system. We are particularly grateful to Rehana Sung for assistance with HPLC purification of compound **5**, **6** and **7** and Dr. Julian Box for his contribution to initial investigations into the synthesis of compound **6**.

References and notes

1. (a) 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; (b) Humphreys, J. L.; Lowes, D. J.; Wesson, K. A.; Whitehead, R. C. *Tetrahedron Lett.* **2004**, *45*, 3429–3432.
2. (a) Brettle, R.; Cross, R.; Frederickson, M.; Haslam, E.; MacBeath, F. S.; Davies, G. M. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1275–1278; (b) Brettle, R.; Cross, R.; Frederickson, M.; Haslam, E.; MacBeath, F. S.; Davies, G. M. *Tetrahedron* **1996**, *52*, 10547–10556.
3. Jiang, S.; Singh, G.; Boam, D. J.; Coggins, J. R. *Tetrahedron: Asymmetry* **1999**, *10*, 4087–4090.
4. See for examples; (a) Card, P. J.; Reddy, G. S. *J. Org. Chem.* **1983**, *48*, 4734–4743; (b) Weigert, F. J.; Shenvi, A. *J. Fluorine Chem.* **1994**, *66*, 19–21.
5. See for examples: Box, J. M.; Harwood, L. M.; Humphreys, J. L.; Morris, G. A.; Redon, P. M.; Whitehead, R. C. *Synlett* **2002**, 358–360.
6. 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.
7. Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625–1627.
8. Alves, C.; Barros, M. T.; Maycock, C. D.; Ventura, M. R. *Tetrahedron* **1999**, *55*, 8443–8456.
9. (a) Saksena, A. K.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273–276; (b) Armesto, N.; Ferrero, M.; Fernández, S.; Gotor, V. *Tetrahedron Lett.* **2000**, *41*, 8759–8762.
10. Typical experimental procedure for tandem dehydration/fluorodeoxygenation. A solution of the diol (0.36 mmol) in CH_2Cl_2 (1 mL) was added dropwise, under an atmosphere of nitrogen, to an ice-cooled solution of dialkylaminosulfurtrifluoride (0.8 mmol) in CH_2Cl_2 (1 mL). Once addition was complete, the ice bath was removed and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and then quenched by the careful addition of a saturated aqueous solution of sodium bicarbonate (10 mL). The organic phase was collected and the aqueous phase was extracted with a further three portions of CH_2Cl_2 (3×10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (SiO_2; EtOAc–petroleum ether (40–60), 1:10) provided the fluorinated products.
11. Spectroscopic data for compound **15b**. Mp 107–109 °C; $[\alpha]_D^{22}$ +14.4 (*c* 10.5, CH_2Cl_2); ν_{max} (film)/cm^{-1} 2992 m, 2952 m, 2916 m and 2834 m (C–H), 1725 s (C=O), 1650 w (C=C); δ_H (400 MHz; $CDCl_3$) 1.33 and 1.40 (2×3H, 2×s, 2×butyl CH_3), 2.35 (1H, dddd, *J* 18.1, 15.0, 10.2, 2.7 Hz, C(6)H_β), 2.93 (1H, dtd, *J* 18.1, 6.2, 0.9 Hz, C(6)H_α), 3.29 and 3.30 (2×3H, 2×s, 2×acetal OCH_3), 3.70 (1H, ddd, *J* 24.5, 11.1, 3.6 Hz, C(4)*H*), 3.79 (3H, s, CO_2 CH_3), 4.15 (1H, ~td, *J* 10.7, 6.2 Hz, C(5)*H*), 5.10 (1H, ddd, *J* 50.1, 5.2, 3.6 Hz, C(3)*H*F), 6.90 (1H, ddd, *J* 5.2, 2.7, 2.2 Hz, C(2)*H*); δ_C (75.4 MHz; $CDCl_3$) 17.98 and 18.08 (2×butyl CH_3), 30.67 (d, *J* 3.1 Hz, *C*(6)H_2), 48.30 and 48.40 (2×acetal OCH_3), 52.63 (CO_2 CH_3), 62.72 (*C*(5)H), 69.95 (d, *J* 17.0 Hz, *C*(4)H), 84.17 (d, *J* 175.5, *C*(3)HF), 99.48 and 100.38 (2×acetal *C*), 130.96 (d, *J* 13.5 Hz, *C*(2)H), 135.20 (d, *J* 9.8 Hz, *C*(1)), 166.38 (*C*=O); δ_F (376.3 MHz; $CDCl_3$) −180.2 (ddddd, *J* 50.1, 24.5, 15.0, 6.2, 2.2 Hz, C(3)H*F*); *m/z* (CI/NH_3) 322 (MNH_4^+, 12%), 290 (82), 273 (88), 270 (30), 258 (30), 241 (30), 85 (100); (found 322.1669: $C_{14}H_{25}FNO_6$ (MNH_4^+) requires 322.1666).
12. A definitive mechanistic explanation for the formation of **16b** is not possible, however it is plausible that the reaction may procceed via an oxetane intermediate, which undergoes nucleophilic ring opening at C1.
13. Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M.; Cheng, H. *J. Org. Chem.* **1999**, *64*, 7048–7054.
14. Crystallographic data (excluding structure factors) for structure **16a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publica-

tion number CCDC 235040. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

15. Crystal structure data for **16a**: $C_{16}H_{25}FO_7$, $M = 348.36$, monoclinic, spacegroup C2, $a = 28.00(4)$, $b = 8.323(11)$, $c = 15.61(2)$ Å, U = 3573 Å^3, $d_{calcd} = 1.295\,g\,cm^{-3}$. 6257 independent reflections, $R1 = 0.0736$, $wR2 = 0.1918$ for 3449 reflections with $I > 2\sigma(I)$.
16. Spectroscopic data for compound **17b**. $[\alpha]_D^{22}$ +131.2 (*c* 7.5, CH_2Cl_2); ν_{max} (film)/cm^{-1} 2994 m, 2953 m, 2836 m (C–H), 1725 s (C=O), 1654 w (C=C); δ_H (400 MHz; $CDCl_3$) 1.32 and 1.35 (2×3H, 2×s, 2×butyl CH_3), 2.31–2.41 (1H, m, C(6)H_β), 2.76 (1H, dd, *J* 17.6, 6.0 Hz, C(6)H_α), 3.27 and 3.31 (2×3H, 2×s, 2×acetal OCH_3), 3.78 (3H, s, CO_2 CH_3), 3.78–3.95 (2H, m, C(4)*H* and C(5)*H*), 5.21 (1H, ddddd, *J* 49.6, 7.6, 3.6, 2.4, 1.4 Hz, C(3)*H*F), 6.76 (1H, dt, *J* 11.2, 2.4 Hz, C(2)*H*); δ_C (100 MHz; $CDCl_3$) 17.69 and 17.72 (2×butyl *C*H_3), 29.35 (d, *J* 2.3 Hz, *C*(6)H_2), 48.04 and 48.08 (2×acetal O*C*H_3), 52.29 (CO_2 *C*H_3), 64.77 (d, *J* 9.1 Hz, *C*(5)H), 71.88 (d, *J* 17.4 Hz, *C*(4)H), 89.34 (d, *J* 171.5 Hz, *C*(3)HF), 99.16 (2×acetal *C*, coincident), 130.76 (d, *J* 9.1 Hz, *C*(1)), 133.68 (d, *J* 22.0 Hz, *C*(2)H), 165.69 (*C*=O); δ_F (376.3 MHz; $CDCl_3$) −184.90 (dddd, *J* 49.6, 16.6, 11.2, 6.4 Hz, C(3)H*F*); *m*/*z* (CI/NH_3) 322 (MNH_4^+, 2%), 290 (80), 273 (100), 258 (35), 241 (30); (found 322.1665: $C_{14}H_{25}FNO_6$ (MNH_4^+) requires 322.1666).
17. Mitsunobu, O. *Synthesis*, **1981**, 1–28.
18. Allylic alcohol **21** can also be prepared by face-selective reduction of enone **22** using either DIBAL-H[8] or Luche reduction conditions.[19] In both cases, approximately 7% of the epimeric alcohol **20** is also formed.
19. Banwell, M. G.; Edwards, A. J.; Essers, M.; Jolliffe, K. A. *J. Org. Chem.* **2003**, *68*, 6839–6841.
20. When DAST was used in place of DeoxoFluor® for this procedure, *gem*-difluoride **23** was obtained in 63% yield contaminated with 11% of the diastereoisomers **24**.
21. Spectroscopic data for compound **5**. $[\alpha]_D^{22}$ −160.4 (*c* 9.10, H_2O); δ_H (300 MHz; D_2O) 2.03–2.20 (1H, m, one of C(6)H_2), 2.68 (1H, ∼dt, *J* 18.3, 5.2 Hz, one of C(6)H_2), 3.76 (1H, ddd, *J* 17.7, 8.6, 3.6 Hz, C(4)*H*), 3.88–3.99 (1H, m, C(5)*H*), 5.13 (1H, dt, *J* 47.4, 3.6 Hz, C(3)*H*F), 6.79 (1H, br s, C(2)*H*); δ_C (75.4 MHz; D_2O) 30.79 (*C*(6)), 66.21 (d, *J* 2.4 Hz, *C*(5)H), 70.08 (d, *J* 16.5 Hz, *C*(4)H), 86.89 (d, *J* 166.6 Hz, *C*(3)HF), 131.91 (d, *J* 17.1 Hz, *C*(2)H), 133.14 (d, *J* 9.8 Hz, *C*(1)), 169.22 (*C*=O); δ_F (376.3 MHz; D_2O) −53.20 (br d, *J* 47.4 Hz, C(3)H*F*); *m*/*z* (negative ion electrospray) 175 (100%, $[M-H]^-$), 155 (68), 111 (28); (found 175.0398, $C_7H_8O_4F$ ($[M-H]^-$) requires 175.0401).